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By Authority of the
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Express Mail Label No. EV 233500225 US
Attorney Docket No. PHA 3483(4152)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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[ ] Additional inventors are being named on the ___ separately numbered sheet(s) attached hereto.

Title of the Invention: STEROID SPIROLACTONIZATION

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ENCLOSED APPLICATION PARTS:

[X] Specification - Number of Pages 64

[ ] Drawings - Number of Sheets ______

[X] Application Data Sheet

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[X] Return Receipt Postcard

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No
[ ] Yes, the name of the U.S. Government agency and the Government contract number are: ______________

Respectfully submitted,

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Date: March 21, 2003

JED/clh

APPLICATION DATA SHEET

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Express Mail Label No. EV 233500225 US

PHA 3483(4152)
PATENT

STEROID SPIROLACTONIZATION

BACKGROUND OF THE INVENTION

This invention generally relates to processes for preparing steroid compounds, and more particularly, to processes for preparing steroid compounds having a spirolactone functional group at the C-17 position. In certain preferred embodiments, the invention relates to novel processes for the C-17 spirolactonization of steroid compounds, and novel intermediates produced therein, which are useful in the preparation of methyl hydrogen 9,11α-epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-lactone (otherwise referred to as eplerenone or epoxymexrenone).

Methods for the preparation of 9,11 epoxy steroids in general, and eplerenone in particular, are described in International Publication WO 98/25948 and U.S. Patent No. 6,331,622, U.S. Patent No. 6,180,780 and U.S. Patent No. 5,981,744, the entire texts of which are hereby incorporated herein by reference. Additional methods for preparing 9,11 epoxy steroids, and eplerenone in particular, are described in co-assigned U.S. Patent Application Serial No. ____________, entitled "Processes To Prepare Eplerenone", filed on even date herewith and hereby incorporated herein by reference in its entirety. Further, methods for preparing C-17 spirolactone steroid compounds are also described in co-assigned U.S. Patent Application Serial No. ____________, filed on even date herewith and hereby incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

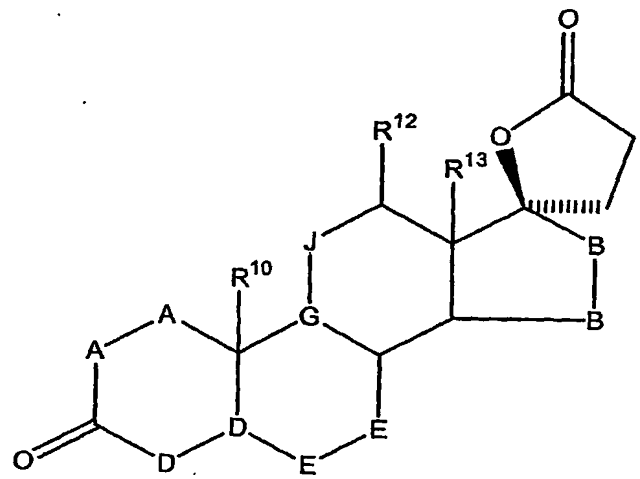
This invention provides for, in part, novel processes for the C-17 spirolactonization of steroid compounds and novel steroidal compositions produced as intermediates therein.

Accordingly, in a first embodiment, the present invention is directed to a process for the preparation of a 17-spirolactone steroid compound. The process comprises carbonylating a steroid substrate which is substituted at the C-17 position with a first substituent selected from the group consisting of hydroxy and protected hydroxy; and a second substituent selected from the group consisting of alkenyl and alkynyl.

In another embodiment, the present invention is directed to a process for the preparation of a 17-spirolactone steroid compound. The process comprises reducing the 17-alkynyl group of a 17-alkynyl-17-hydroxy steroid compound to produce a 17-alkenyl-17-hydroxy steroid compound. The process further comprises carbonylating the 17-alkenyl-17-hydroxy steroid compound to produce the 17-spirolactone steroid compound.

In another embodiment, the present invention is directed to a process for the preparation of a 17-spirolactone steroid compound. The process comprises carbonylating a 17-alkynyl-17-hydroxy steroid compound to produce a steroid intermediate comprising a 17-lactenone steroid compound. The process further comprises reducing the 17-lactenone steroid compound of the intermediate to produce a 17-spirolactone steroid compound.

In another embodiment, the present invention is further directed to a process for the preparation of a compound corresponding to the Formula 1503:

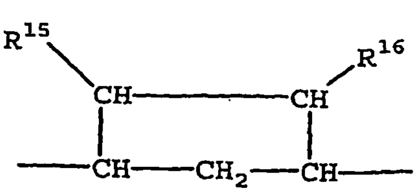


wherein

R^{10}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, hydroxy, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano and aryloxy;

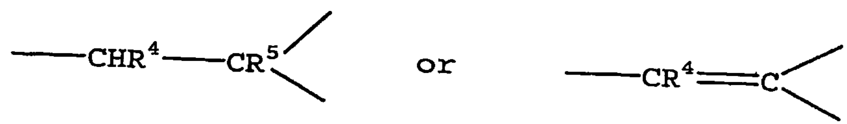
A-A represents the group CHR^1-CHR^2 or CR^1=CR^2, where R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^1 and R^2 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

B-B represents the group CHR^{15}-CHR^{16} or an alpha- or beta- oriented group:



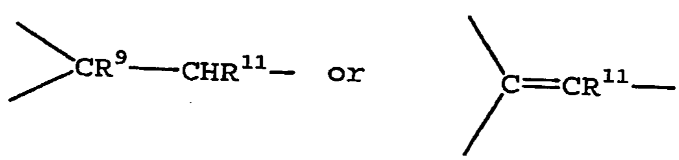
where R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, and aryloxy;

D-D represents the group



where R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^4 and R^5 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

G-J represents the group

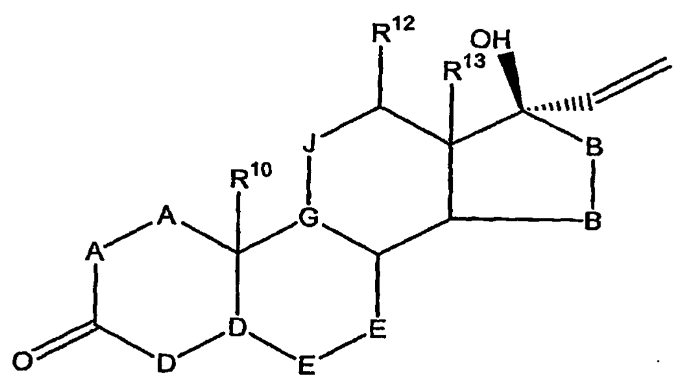


where R^9 and R^{11} are independently selected from the group consisting of hydrogen, hydroxy, protected hydroxy, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^9 and R^{11} together form an epoxy group;

E-E represents the group $-CHR^6-CHR^7-$ or $-CR^6=CR^7-$, wherein R^6 and R^7 are independent, R^6 being selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl,

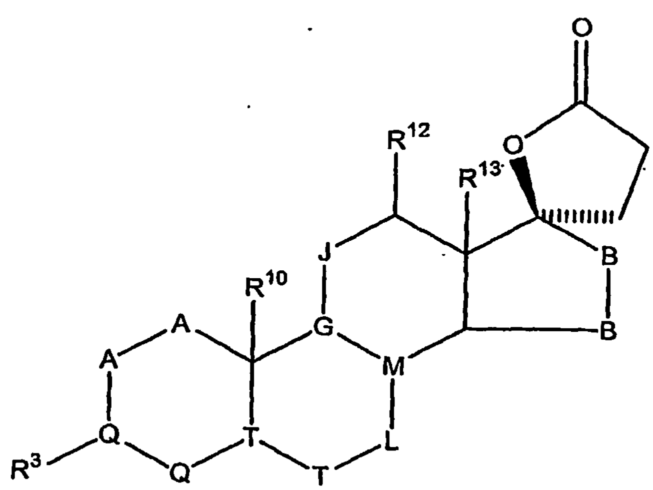
hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy, and R^7 being selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, aryloxy, heteroaryl, heterocyclyl, thioacetyl, furyl and substituted furyl.

The process comprises carbonylating a 17-vinyl-17-hydroxy steroid compound of Formula 1502:



wherein R^{10}, R^{12}, R^{13}, A-A, B-B, D-D, G-J and E-E are as defined above in Formula 1503.

In another embodiment, the present invention is directed to a process for the preparation of a compound corresponding to the Formula 2503:



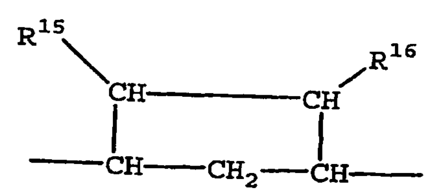
wherein

R^3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl and hydroxycarbonyl;

R^{10}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano and aryloxy;

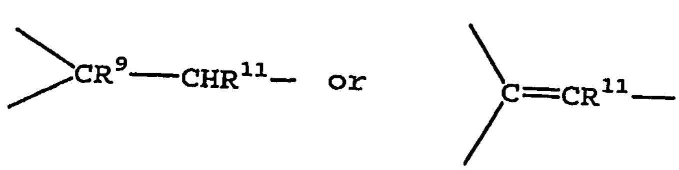
A-A represents the group $-CHR^1-CHR^2-$ or $-CR^1=CR^2-$, where R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^1 and R^2 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

B-B represents the group $-CHR^{15}-CHR^{16}-$ or an alpha- or beta- oriented group:



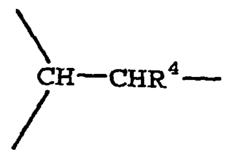
where R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

G-J represents the group



where R^9 and R^{11} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

Q-Q represents the group



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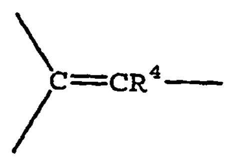
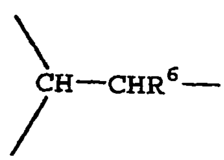


where R^4 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

T-T represents the group



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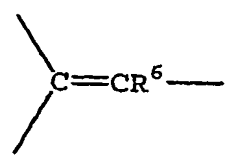
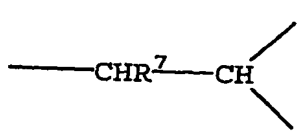


where R^6 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy; and

L-M represents the group



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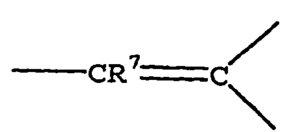
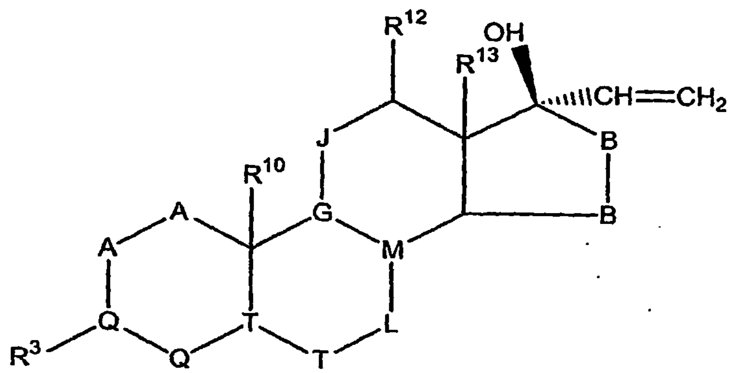


where R^7 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, alkoxy, acyl,

hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, aryloxy, heteroaryl, heterocyclyl, thioacetyl, furyl and substituted furyl.

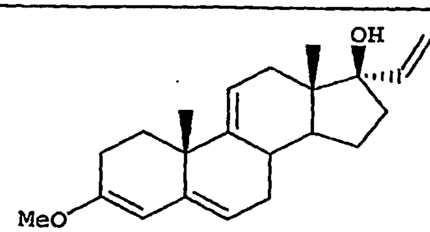
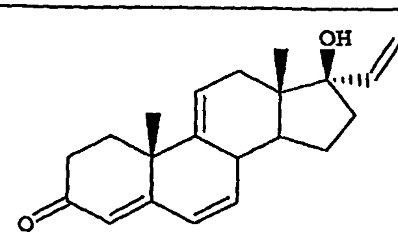
The process comprises carbonylating a 17-vinyl-17-hydroxy steroid compound of Formula 2502:

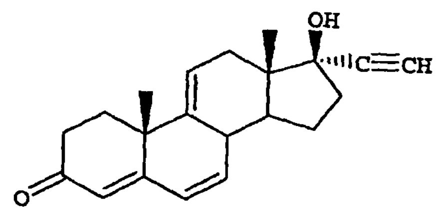
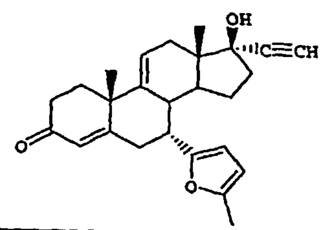
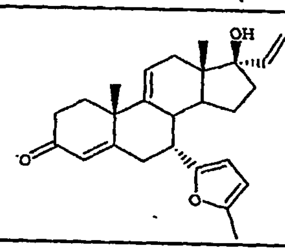


where the substituents R^3, R^{10}, R^{12}, R^{13}, A-A, B-B, G-J, Q-Q, T-T and L-M are as defined above in Formula 2503.

Still further, the present invention is directed to novel steroid compounds set forth in Table I.

TABLE I

Formula A	
Formula B	

Formula C	
Formula D	
Formula E	

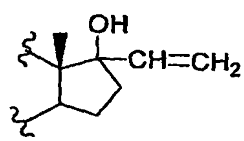
Other objects of the invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

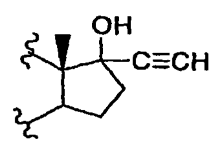
In accordance with the present invention, Applicants have discovered a process for the preparation of steroid compounds having a spirolactone functional group at the C-17 position. The process of the present invention generally comprises a carbonylation and a selective hydrogenation of a steroid substrates. An advantage of the process is that the carbonylation and selective hydrogenation reactions may be conducted as isolated steps, in either order, or in situ in a single reaction zone. Further, as is demonstrated below, certain preferred embodiments of the invention provide novel processes for the preparation of epoxymexrenone (methyl hydrogen 9,11α-epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-lactone).

Steroid Substrate

Steroid substrates for use as starting materials in processes of the present invention generally comprise steroid compounds substituted at the C_{17}-position with a first substituent selected from the group consisting of hydroxy and protected hydroxy; and a second substituent selected from the group consisting of alkenyl and alkynyl. In preferred embodiments, the steroid substrates are substituted at the C_{17} position with a first substituent comprising a hydroxy group and a second substituent comprising an alkenyl or an alkynyl group, more preferably a second substituent comprising a vinyl or an ethynyl group:

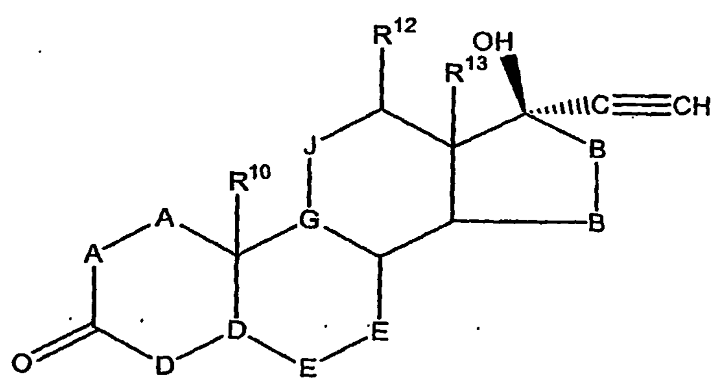


17-vinyl



17-ethynyl

In a first embodiment, the steroid substrate comprises a 17-hydroxy, 17-ethynyl steroid comprising a compound of Formula 1501:



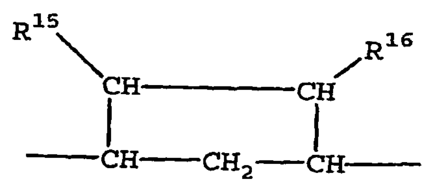
wherein:

R^{10}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, hydroxy,

alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano, and aryloxy;

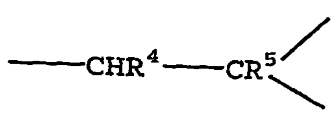
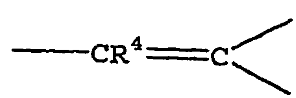
A-A represents the group CHR^1-CHR^2 or CR^1=CR^2, where R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, cyano and aryloxy; or R^1 and R^2 together with the carbon atoms of the steroid backbone to which they are attached from a cycloalkyl group;

B-B represents the group CHR^{15}-CHR^{16} or an alpha- or beta- oriented group:



where R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, and aryloxy;

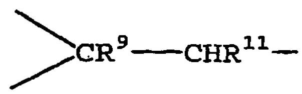
D-D represents the group

 or 

where R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^4

and R^5 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group; and

G-J represents the group



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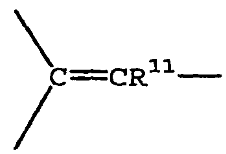
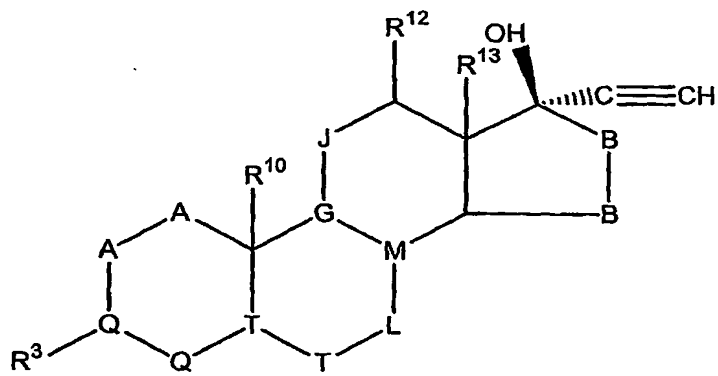
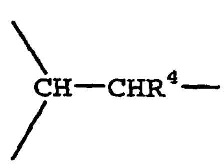


In another embodiment, the steroid substrate comprises a 17-hydroxy, 17-ethynyl steroid comprising a compound of Formula 2501:



wherein

Q-Q represents the group



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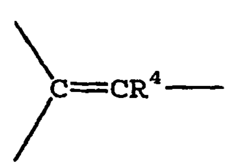
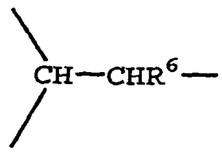


where R^4 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

T-T represents the group



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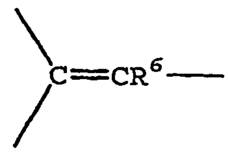
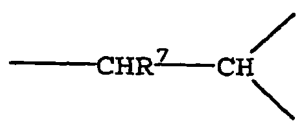


where R^6 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy; and

L-M represents the group



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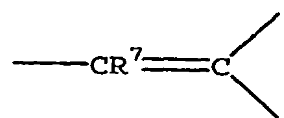
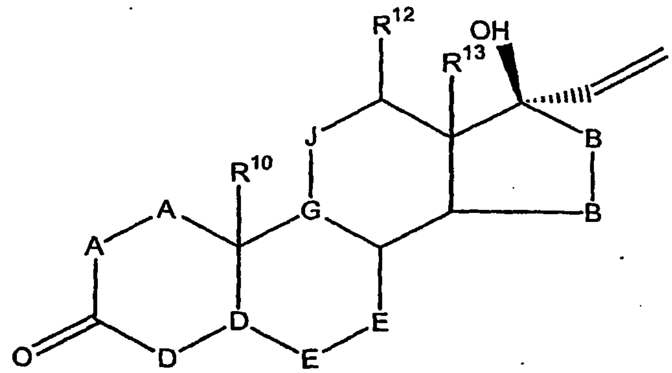


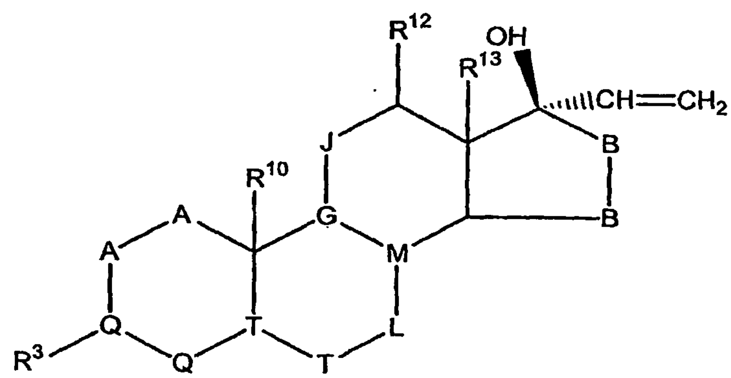
where R^7 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, aryloxy, heteroaryl, heterocyclyl, thioacetyl, furyl and substituted furyl.

In still another embodiment, the steroid substrate comprises a 17-hydroxy, 17-vinyl steroid comprising a compound of Formula 1502:



wherein the substituents R^{10}, R^{12}, R^{13}, A-A, B-B, D-D, G-J, and E-E are as defined above in Formula 1501.

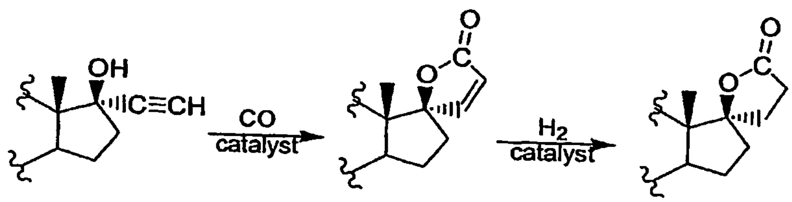
In another embodiment, the steroid substrate comprises a 17-hydroxy, 17-vinyl steroid comprising a compound of Formula 2502:



wherein the substituents R^{10}, R^{12}, R^{13}, A-A, B-B, AND G-J are as defined in Formula 1501 and Q-Q, T-T, L-M, and R^3 are as defined in Formula 2501.

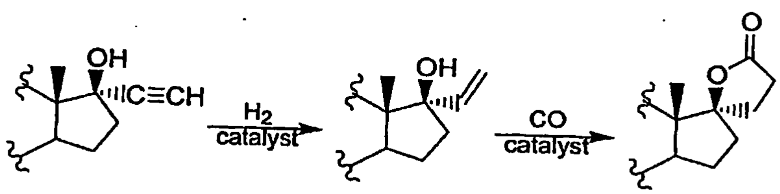
As described above, the process of the present invention generally comprises the steps of carbonylation and selective hydrogenation to incorporate a spirolactone functional group at the C_{17} position of a steroid compound. An advantage of the process is that the carbonylation and selective hydrogenation reactions may be conducted as isolated steps, in either order, or in situ in a single

reaction zone, thereby providing a flexible method which may be utilized on a wide variety of substrates as described above. For example, in a certain preferred embodiment beginning with a 17-ethynyl steroid substrate, the process may comprise two reaction sequences including a carbonylation followed by a hydrogenation as shown in Reaction Scheme A or a hydrogenation followed by a carbonylation as shown in Reaction Scheme B.



17-ethynyl 17-lactenone 17-spiro

Reaction Scheme A



17-ethynyl 17-vinyl 17-spiro

Reaction Scheme B

A. Carbonylation

In one embodiment, the process of the present invention comprises carbonylating steroid substrates substituted at the C-17 position. Generally, the carbonylation reaction comprises contacting the steroid substrate with a source of carbon monoxide and a carbonylation catalyst. Typically, the carbonylation catalyst comprises a metal catalyst, preferably a catalyst comprising a metal selected from the group consisting of Co, Ni, Fe, Pt, Pd, Ru, Rh, Ir and mixtures thereof, with Pd being preferred in certain embodiments.

In accordance with the present invention, it has further been discovered that an active carbonylation catalyst species can be generated in situ in the carbonylation reaction medium. In one embodiment, the carbonylation catalyst is formed by contacting a source of a metal with a source of carbon monoxide. In other preferred embodiments the catalyst may be formed by contacting a source of metal with carbon monoxide in the presence of a ligand and/or a reducing agent.

When the catalyst comprises palladium, suitable palladium sources may comprise palladium acetate, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, PdO, and Pd/C. For example, palladium on carbon has been used successfully in carbonylation reactions as a source of the *homogeneous* catalytic species. However, use of Pd/C generates a spent carbon support that must be later removed from the product mixture by filtration. Thus, in certain embodiments, palladium acetate is preferred because of its stability, availability, cost, reliability, and versatility.

Further, in embodiments wherein the metal catalyst comprises a source of Pd, it may be preferred to contact the metal with a ligand such as a ligand containing phosphorus. Examples of suitable phosphorus containing ligands include phosphine ligands, preferably phosphine ligands selected from the group consisting of dppb, bdpp, dppf, BIPHEPHOS, DPEphos, and xantphos.

Suitable reducing agents for use in forming the catalyst may generally comprise any active hydrogen source known to those skilled in the art, with active hydrogen sources such as hydrogen, formic acid, borohydrides and oxalic acid being preferred in some embodiments.

The carbonylation may further be conducted in the presence of a solvent. For example, suitable solvents typically comprise solvents selected from the group

consisting of methylene chloride, tetrahydrofuran, ethyl acetate, acetonitrile, dimethylether, dioxane, toluene, dimethylformamide and mixtures thereof.

B. Hydrogenation

In another embodiment, the process of the present invention comprises the selective hydrogenation of 17-alkynyl steroids as defined above. Generally, the process comprises contacting the steroid substrate with a source of hydrogen, more preferably in the presence of a catalyst.

Preferred catalysts for the hydrogenation reaction typically comprise noble metal catalysts, such as noble metal catalysts supported on carbon or calcium carbonate supports. An example of a certain preferred noble metal catalyst comprises palladium on a calcium carbonate support such as a "Lindlar" catalyst. Lindlar catalysts are known in the art and available commercially, for example, from Johnson Matthey and Sigma Aldrich. A preferred type of Lindlar catalyst is Johnson Matthey type A310050-5 comprising 5% by weight Pd on a calcium carbonate support poisoned by lead.

When the catalyst comprises a noble metal on a support, it is conceived that the catalyst may be recovered from the hydrogenation reaction medium, for example, by filtration. The recovered noble metal catalyst may then be recycled and reused in subsequent hydrogenation reaction. Experience to date has suggested that catalyst can be removed from the product mixture using vacuum filtration through a fine-porosity sintered glass filter. It is conceived that filtration of the catalyst could be made more efficient for commercial application, for example, using pressure filtration through a sintered metal filter.

The hydrogenation reaction may be further conducted in the presence of a solvent. Examples of suitable solvents

include methanol, dichloromethane, acetone, acetonitrile, ethyl acetate, THF, DME, and DMF.

The hydrogenation reaction is typically conducted at elevated pressure. For example, hydrogen is preferably added to the reactor headspace and supplied on demand to maintain a total system pressure of from about 0 to about 100 psig, preferably from about 25 to about 50 psig. The reaction is typically conducted at a temperature of from about 0° to about 100°C, preferably at a temperature of from about 25° to about 75°C.

In certain preferred embodiments, the hydrogenation reaction is conducted in the presence of a sacrificial reduction target. For example, experience to date suggests that when the steroid substrate comprises a steroid saturated at the C_9/C_{11} position, a sacrificial reduction target may be added to the hydrogenation reaction medium to prevent over-reduction of the steroid substrate. For example, without being held to a particular theory, it has been found that the addition of an adjuvant such as an alkene or cycloalkene to the reaction mixture tends to increase the tolerance of the steroid to over-reduction. In contrast, it has been unexpectedly discovered that $\Delta^{9(11)}$ steroid substrates possess an inherent resistance to over-reduction. Thus, rigorous endpoint determination and/or use of adjuvants to suppress reduction of the desired 17-vinyl steroid product may not necessarily be required.

C. In Situ Carbonylation and Hydrogenation

As previously stated, it has been found that the carbonylation and hydrogenation reactions described above can be conducted in any order or in a single reactor as an in situ carbonylation/hydrogenation to produce a C-17 spirolactone steroid compound.

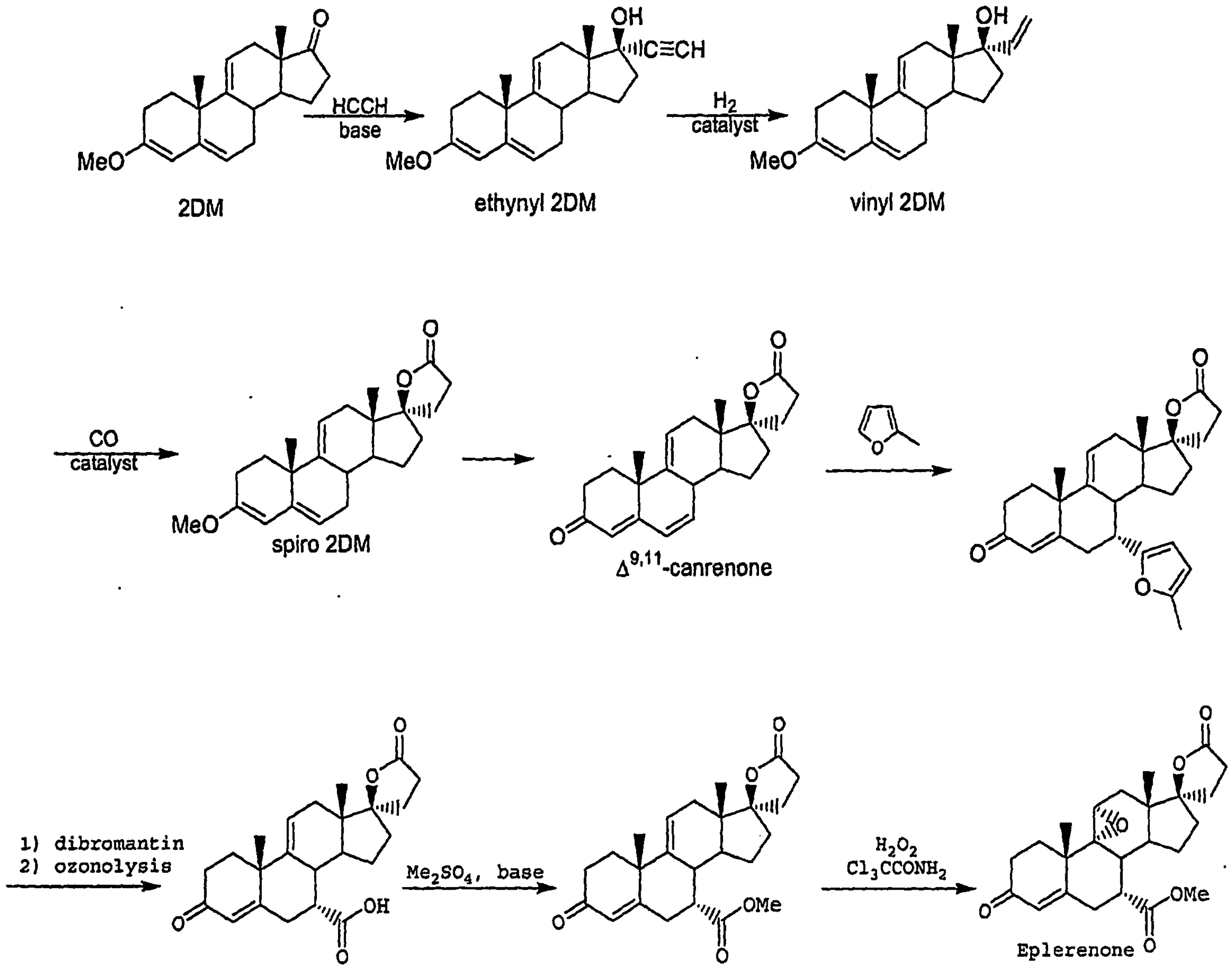
Thus, in one embodiment, the process of the present invention comprises simultaneously contacting the steroid substrate with a source of hydrogen, a source of carbon monoxide and a catalyst system effective for reducing the 17-ethynyl group and for carbonylating the resulting derivative in situ to convert the derivative to a 17-spirobutyrolactone structure.

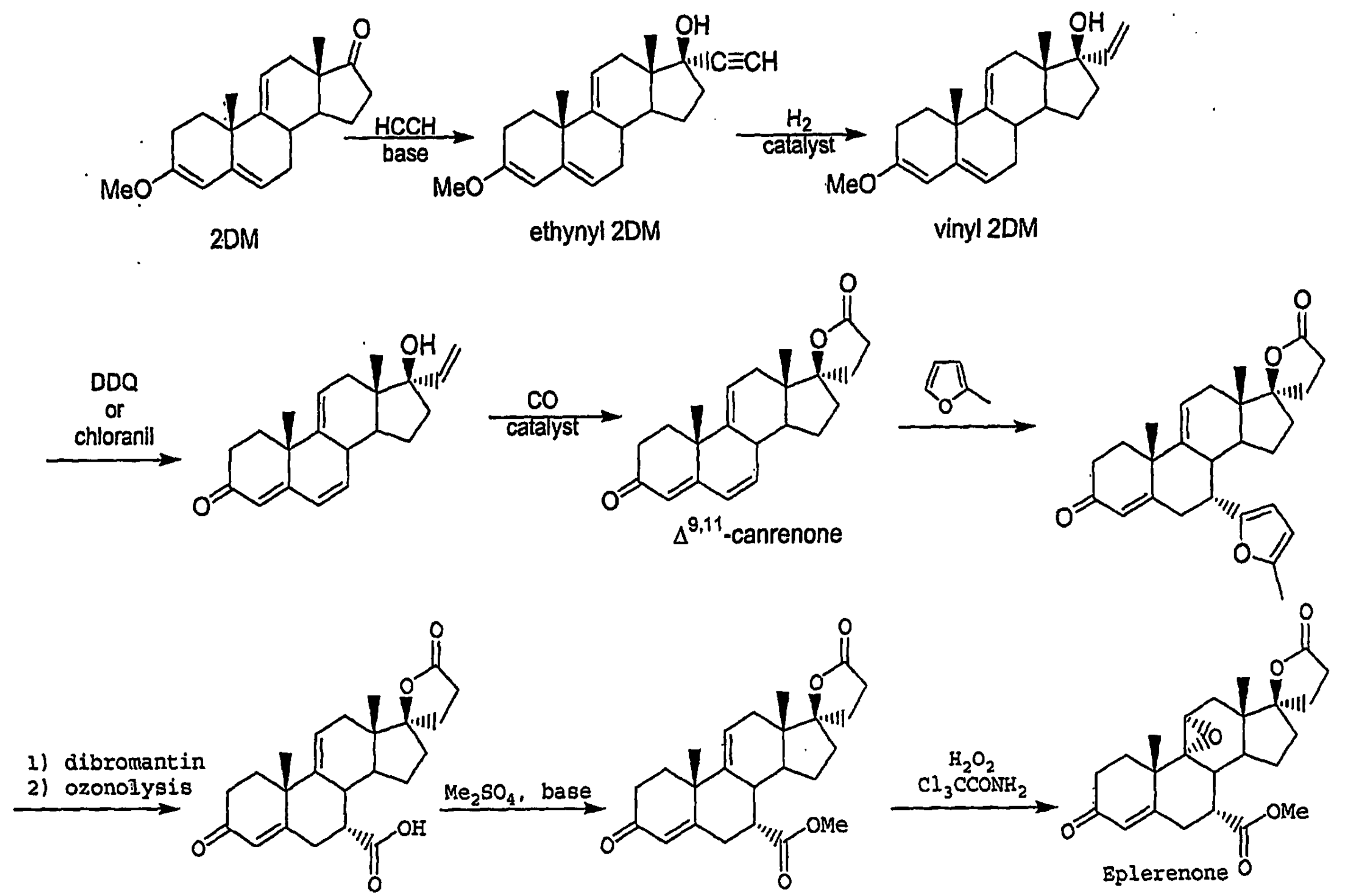
Overall Process

As described above and shown in Reaction Schemes I to VI, further embodiments of the present invention are directed to novel processes for the preparation of methyl hydrogen 9,11α-epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-lactone (i.e., eplerenone or epoxymexrenone).

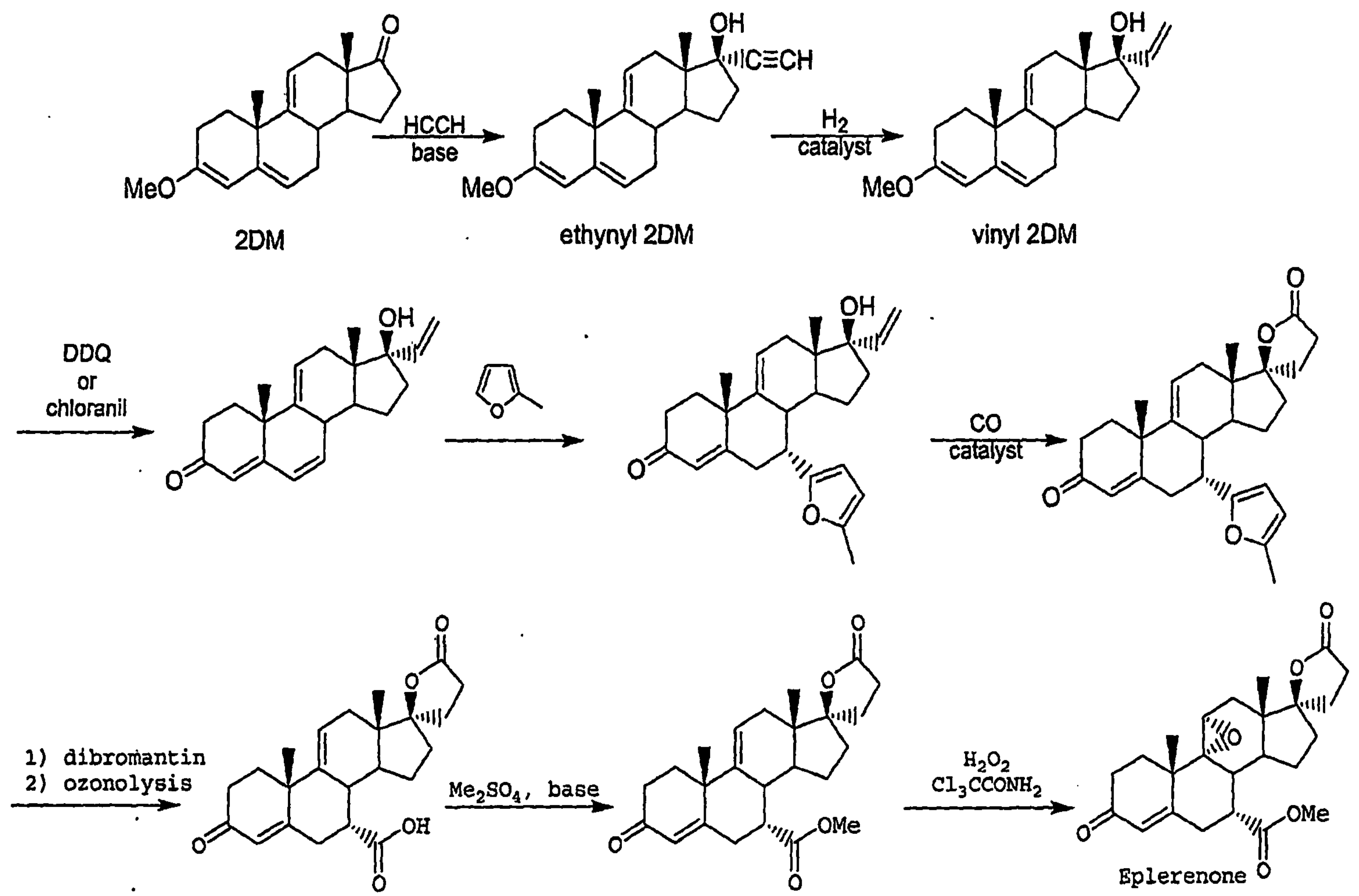
For example, as shown in Reaction Scheme I, a novel process for the preparation of Eplerenone involves the ethynylation of a 2DM substrate to produce an ethynyl 2DM steroid compound. The ethynyl 2DM compound is subsequently semi-hydrogenated, preferably by contact with a source of hydrogen, to produce a vinyl 2DM steroid compound. The vinyl 2DM steroid compound is then carbonylated as described herein to produce an enol ether steroid compound, (17α)-pregna-3,5,9(11)-triene-21-carboxylic acid γ-lactone. The process further comprises oxidizing the enol ether steroid compound, preferably by contact with an oxidizing agent in the presence of water, to produce $\Delta^{9,11}$ canrenone. The $\Delta^{9(11)}$-canrenone is then contacted with an alkyl furan and a Lewis acid to produce a 7α-furyl intermediate compound of Formula VII. The 7α-furyl intermediate compound of Formula VII is oxidized to the 7α-methoxycarbonyl intermediate compound of Formula IX, which is then converted to the epoxymexrenone steroid product. Methods for converting steroid compounds of Formula VII to Eplerenone are more fully described in co-

assigned U.S. Patent Application Serial No. ____________ (entitled "Processes to Prepare Eplerenone", filed on even date herewith and incorporated by reference herein in its entirety). Further, methods for the oxidation of the enol ether substrate are more fully described in co-assigned U.S. Patent Application Serial No. ______ (entitled "C-17 Spirolactonization and 6,7 Oxidation of Steroids," filed on even date herewith and incorporated by reference herein in its entirety).

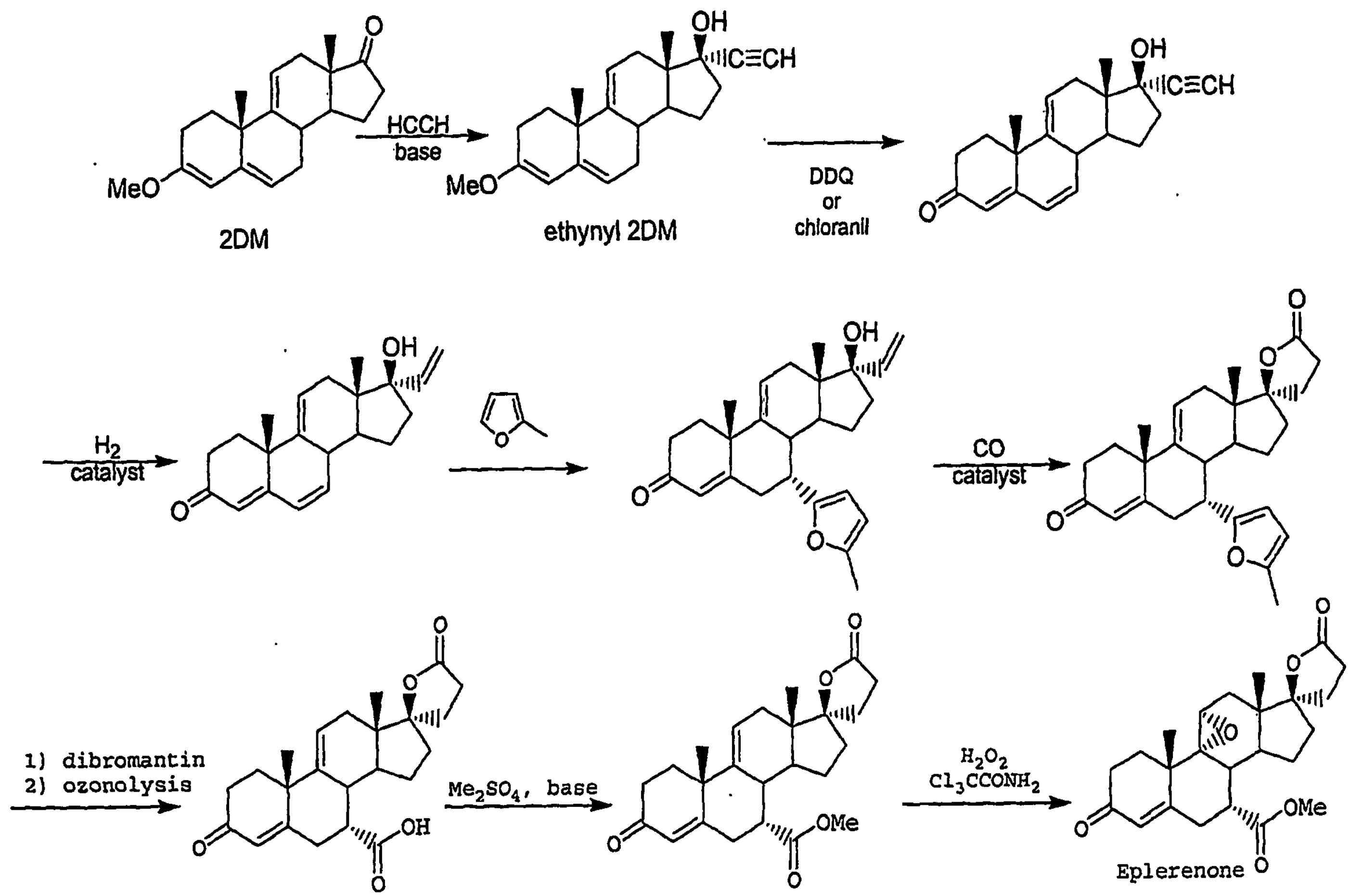

HCCH
base
H2
catalyst
2DM
ethynyl 2DM
vinyl 2DM
CO
catalyst
spiro 2DM
Δ9,11-canrenone
1) dibromantin
2) ozonolysis
Me2SO4, base
H2O2
Cl3CCONH2
Eplerenone



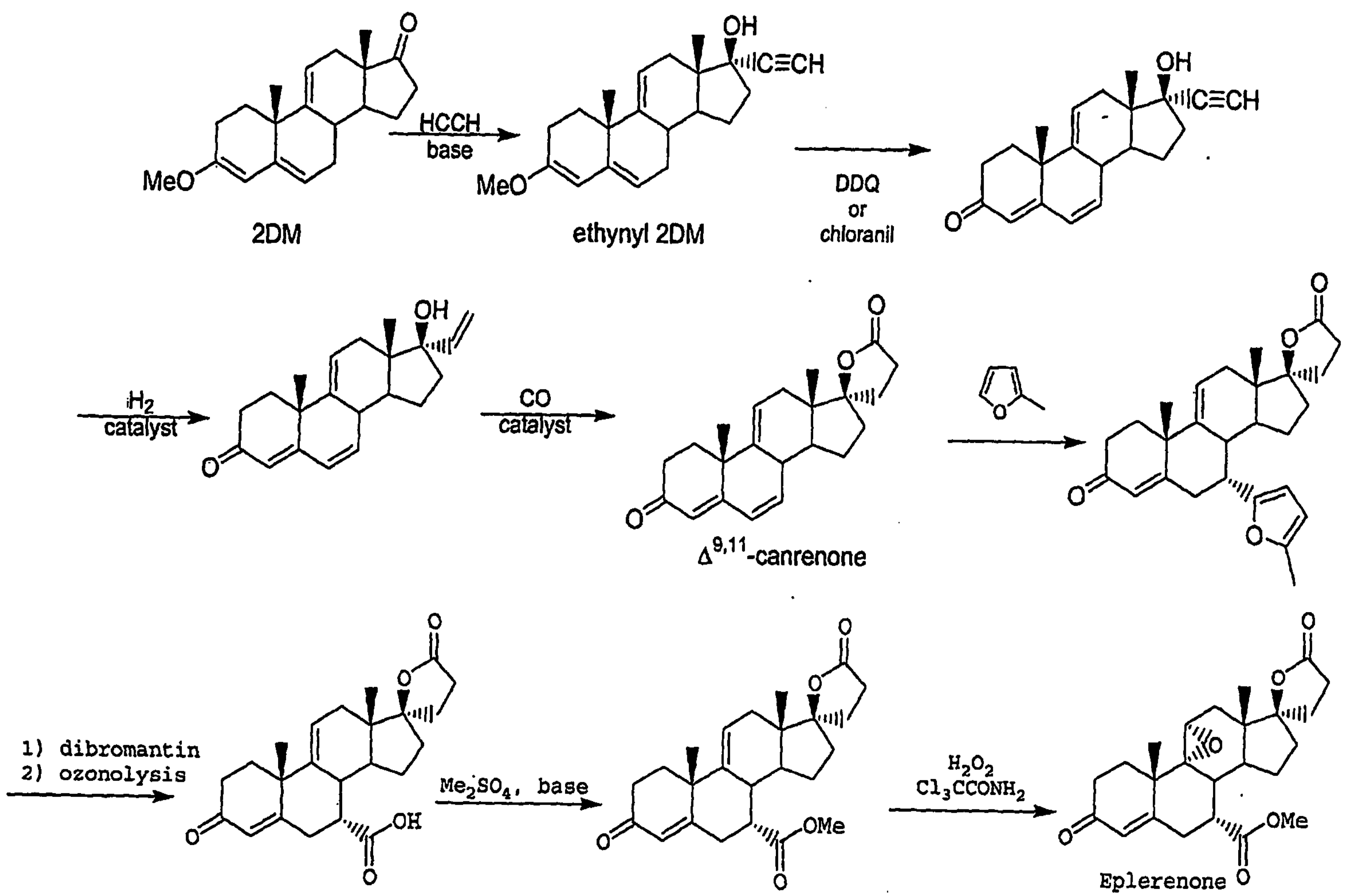
Reaction Scheme II



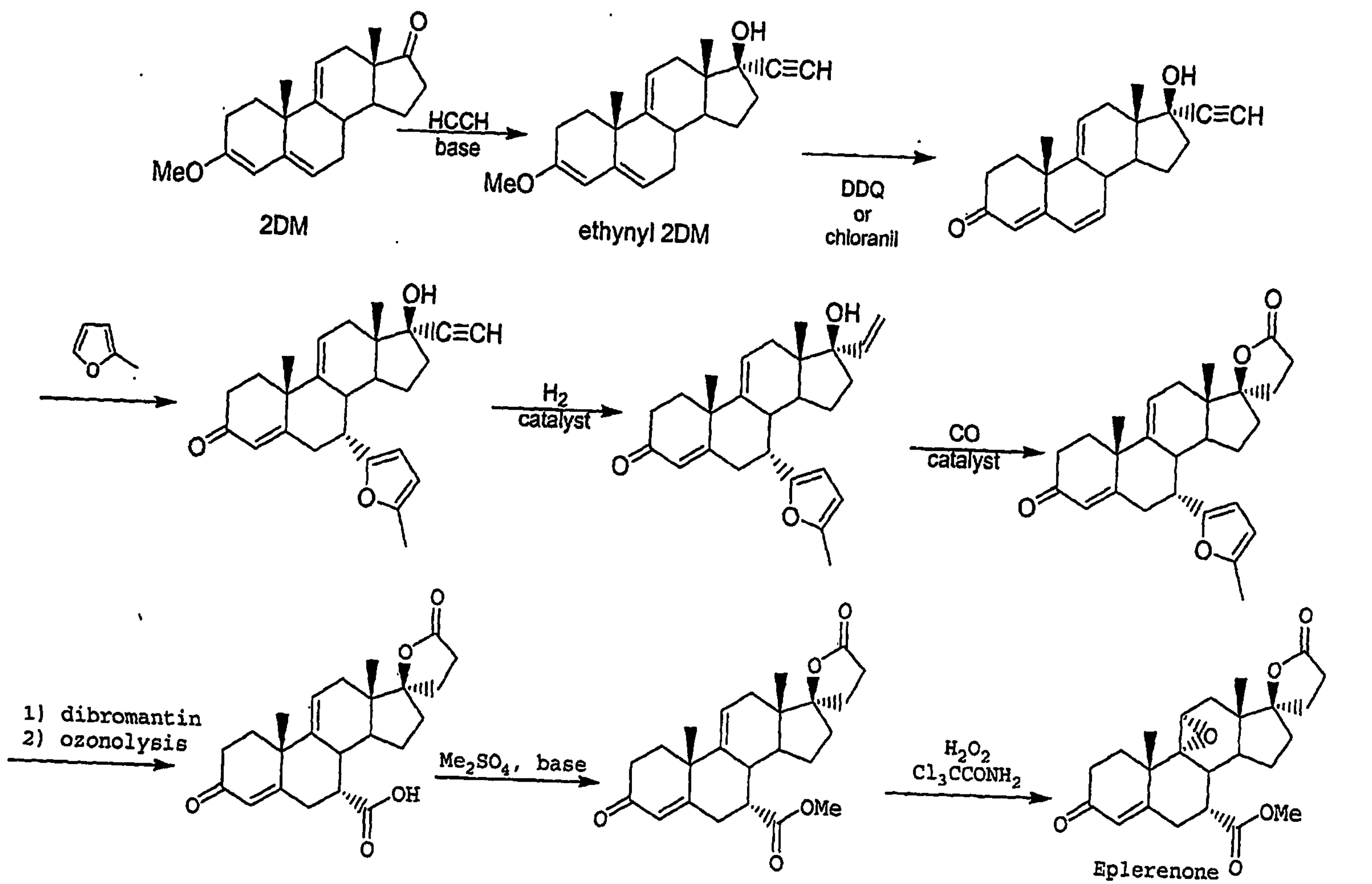
Reaction Scheme III



Reaction Scheme IV



Reaction Scheme V



Reaction Scheme VI

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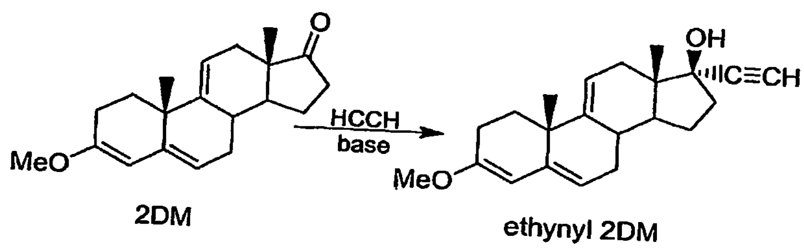
EXAMPLES

The following examples are simply intended to further illustrate and explain the present invention. This invention, therefore, should not be limited to any of the details in these examples.

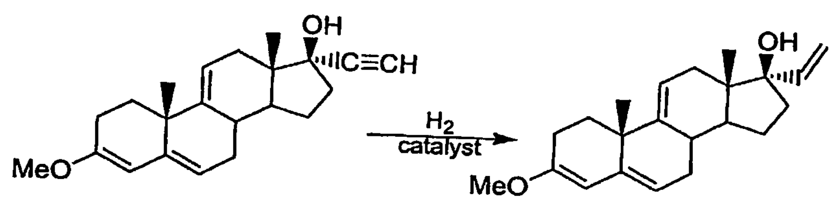
Example 1: Preparation of ethynyl 2DM from 2DM



To a nitrogen-purged 5000 ml flask was charged (300 g) and about 1800 mL BHT-stabilized THF. The slurry was cooled to −13 °C and 1410g of 20% by weight potassium t-butoxide in THF (1550 mL) was added. The homogeneous solution was stirred at -10° to -15°C while acetylene gas is introduced subsurface at a rate of about 5 cubic feet per hour until the reaction was essentially complete by TLC (about 3 hours). The reaction was carefully quenched by the addition of nitrogen-sparged water (120 mL) during which time gas was evolved and the temperature of the mixture rose to about 0°C. The mixture was cooled to -5°C and glacial acetic acid (143.4 g) and methanol (50 mL) were added. Water (about 60 mL) was then added to dissolve the solid salts resulting in the formation of two liquid phases. The lower aqueous phase was removed and discarded. The remaining upper phase was distilled under vacuum with portionwise introduction of methanol (6 × 500 mL) until most of the THF was removed and the final volume of the mixture was 1200 mL. Crystals began

forming during the distillation process and the resulting mixture was cooled to 0 °C. The crystals were then collected by filtration, washed with cold methanol (500 mL), and dried at 25°C under a stream of nitrogen to afford 287.1 g (88.0%) of ethynyl 2DM that was 99.4% pure by HPLC.

Example 2: Scheme 1, Step 2: Selective hydrogenation of ethynyl 2DM to vinyl 2DM

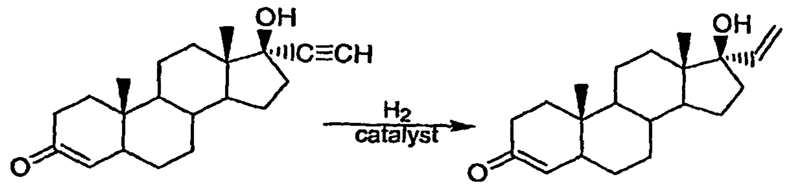


ethynyl 2DM

vinyl 2DM

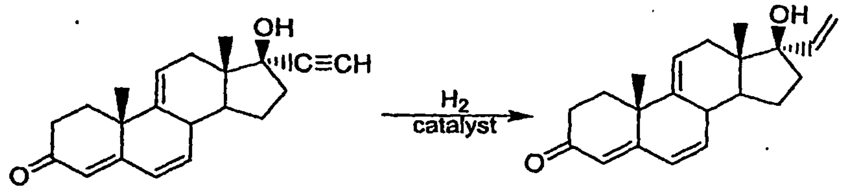
Ethynyl 2DM (25.0 g), methanol (100 mL), triethylamine (0.1 g), and Lindlar catalyst (0.0689 g, Johnson Matthey) were charged to a 300-mL stainless steel Parr autoclave equipped with a standard, four-bladed axial impeller. The reactor was sealed, purged with nitrogen followed by hydrogen, and then pressurized to 40 psig with hydrogen. The mixture was stirred (700 rpm) and heated to 50°C. Hydrogen was fed on demand from a high pressure reservoir of known volume to maintain the total pressure of the reactor at 40 psig. Hydrogen uptake was monitored by following the pressure drop in the hydrogen reservoir. After 1.1 hours, hydrogen uptake ceased. The reactor was vented and the vessel was purged with nitrogen. The reactor contents were vacuum filtered through a fine sintered glass filter using methanol to produce a filtrate (129 g) which contained no ethynyl 2DM starting material and had a ratio of vinyl 2DM to ethyl 2DM of 97.1 to 2.9.

Example 2A: Reduction of 17-ethynyl testosterone to 17-vinyl testosterone



A mixture of ethisterone (50.0 g), Lindlar catalyst (Johnson Matthey, 5% Pd, 0.50 g), methanol (100 g) and 1-hexene (28.5 g) was heated in a 300 mL stirred autoclave under hydrogen (25 psig) for 4.5 hours at 40°C followed by another 1 hour at 60°C. After cooling, the filtered crude product mixture was found to contain 98.3% 17-vinyl testosterone and 1.1% 17-ethyl testosterone by HPLC. Portionwise addition of water (2 volumes) afforded, after drying, 48.84 g of 17-vinyl testosterone 96.7% chemical yield as off-white crystals.

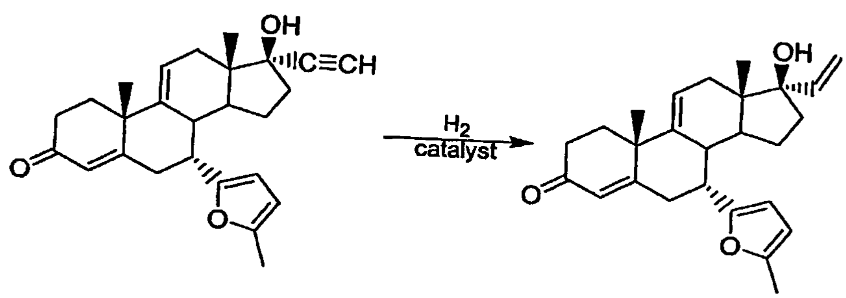
<u>Example 3</u>: Selective hydrogenation of 3-keto, 17-ethynyl to 3-keto, 17-ethynyl



A 50-mL stainless steel autoclave was charged with 3-keto, 17-ethynyl substrate (5.00 g), dichloromethane (20 mL), triethylamine (3 drops), and Lindlar catalyst (Johnson Matthey, type 310050-5, 0.0199 g). The vessel was sealed, purged first with nitrogen and then with hydrogen, and pressurized with hydrogen to 20 psig. Stirring at 400 rpm was then initiated and the reactor was fed hydrogen on-

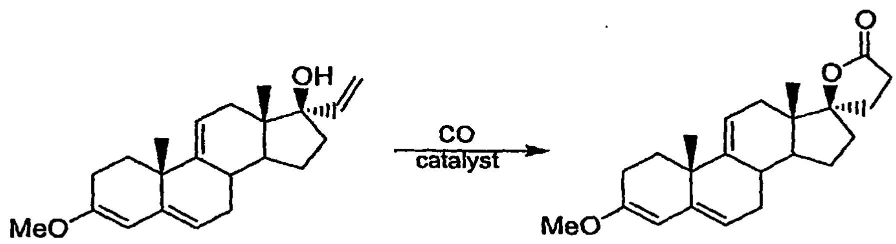
demand from a high pressure reservoir of known volume. After about 6.4 hours, gas consumption essentially ceased and the reactor was carefully vented and purged with nitrogen.

Example 4: Scheme 6, Step 4: Selective hydrogenation of 17-ethynyl, 7-α methylfuryl substrate



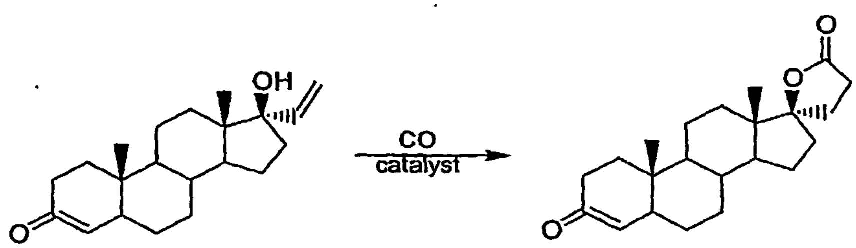
17-ethynyl, 7α-methylfuryl steroid (24.65 g), Lindlar catalyst (Johnson Matthey A310050-5, 0.0871 g), and acetonitrile (100 mL) were charged to a 300-mL autoclave. The vessel was purged with nitrogen followed by hydrogen and then pressurized to 25 psig with H_2. The mixture was heated to a temperature of 50°C while pressure was maintained at 25 psig with hydrogen. When the hydrogen uptake subsided, the reactor pressure was increased to 40 psig, the reaction temperature was increased to 60°C. Additions of Lindlar catalyst (up to 0.4526 g total catalyst present) were required to achieve theoretical hydrogen consumption after about 8 hours. The reaction mixture was then vacuum filtered through a sintered glass filter (fine porosity) with minimal acetonitrile addition to wash the vessel and catalyst. Filtration resulted in 118 g of an acetonitrile solution. HPLC analysis of revealed ca. 98.8% conversion (1.2% starting material) and 99.1% selectivity (0.9 area% of the 17-ethyl as a result of over-reduction).

Example 5: Carbonylation of Vinyl 2DM



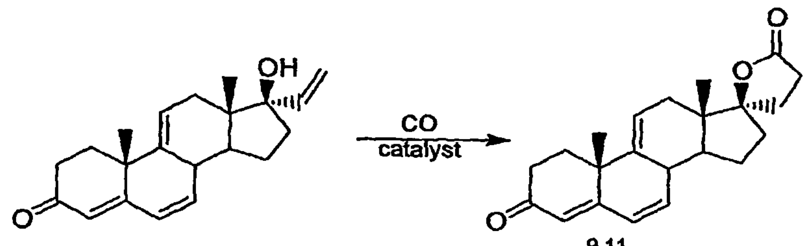
vinyl 2DM spiro 2DM

Example 5A: Carbonylation of 17-vinyl testosterone



17-vinyl testosterone (25.0 g), 10% Pd/C (0.473 g comprising 0.56 mol% Pd), formic acid (7.3 g), 1,4-bis(diphenylphosphino)butane (0.949 g), PPh_3 (0.296 g) and 1,2-dimethoxyethane (163 mL) were charged to a 300-mL autoclave and the mixture was heated at a temperature of 100°C for 18 hours under an atmosphere of carbon monoxide (100 psig). The reactor was then cooled and vented before the crude reaction product mixture was filtered through a pad of silica gel. The product mixture was then washed twice with CH_2Cl_2 (___ mL each wash) and twice with acetone (___ mL each wash). Rotary evaporation of the combined filtrate afforded a thick oil. Et_2O (150 mL) was then added followed by hexanes (300 mL) to afford a white solid, which was subsequently dried. Analysis of the product showed 98.6% by weight yield of aldona.

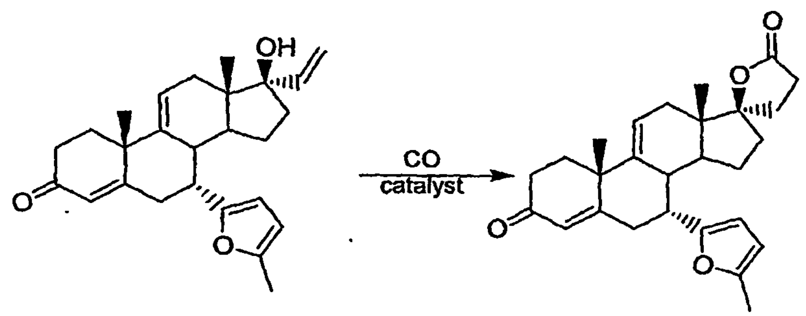
Example 6: Scheme 2, Step 4: Carbonylation



$\Delta^{9,11}$-canrenone

Palladium acetate (0.078 g), DPEphos (0.374 g), and the steroid substrate (crude solution as prepared in Example ___, 21.57 g) were charged to a 300-mL stainless steel reactor under argon and with agitation along with formic acid (96%, 1.6 g), and dry THF (inhibited, 98 mL). The vessel was sealed, purged with 100% CO and pressurized to about 70 psig with CO. After stirring at 25°C for 20 minutes, the mixture was heated to 105°C and the pressure was increased to 100 psig with carbon monoxide. The reactor was fed carbon monoxide on demand from a high pressure reservoir to maintain a total pressure of 100 psig and held for 18 hours at 105°C. After cooling and careful venting, the product mixture was filtered through a plug of silica gel (10 g) to remove some of the palladium and evaporated to dryness. The residue was dissolved in refluxing methanol (70 mL) and water (70 mL) was added dropwise with stirring. The mixture was allowed to cool to 25°C and then placed in a freezer at -10°C. The precipitate was isolated by filtration, washed with cold 1:1 methanol/water (2 x 80 mL), and dried in vacuo at 70°C overnight to afford 22.13 g (94.1% of theoretical mass) of 98.1 wt% pure $\Delta^{9(11)}$-canrenone (See Table 15).. The filtrate and washes were evaporated and dried in vacuo to afford an additional 1.55 g (6.59% of theoretical mass) of 41.1 wt% $\Delta^{9(11)}$-canrenone.

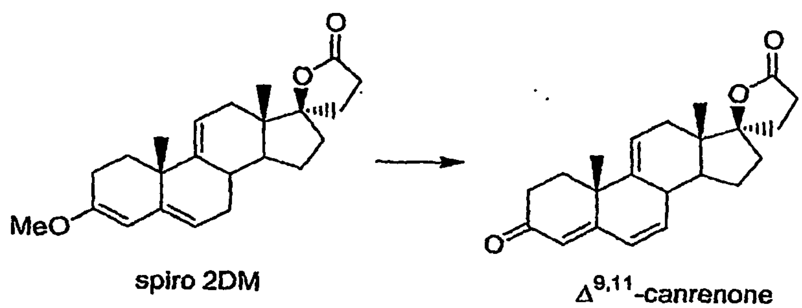
Example 7: Scheme 6, Step 5: Carbonylation



The steroid substrate prepared in Example 4 above (118 g solution containing approximately 23.15 g substrate) was transferred from the filter flask to a 300-mL stainless steel autoclave with the aid of acetonitrile (10 mL). Palladium(II) acetate(0.068 g), 96% formic acid (1.39 g) and 1,4-bis(diphenylphosphino)butane (0.257 g) were then added and the vessel was purged first with nitrogen (3 x 100 psig) followed by carbon monoxide (3 x 100 psig). The reactor was pressurized to 70 psig with CO and stirred at room temperature for 20 minutes before heating to 100°C. The system pressure was adjusted up to and maintained at 100 psig with CO as reactor reached 100°C. After 18 hours at 100°C, the reactor was cooled to room temperature and carefully vented. Filtration of the product mixture through a pad of silica gel (10 g) followed by concentration of the filtrate and acetonitrile washes to gave a crude product that was crystallized from hot acetonitrile (75 mL). After filtration, washing with cold acetonitrile, and drying in vacuo, 16.18 g (65.2% of theory) of steroid product was obtained as a white crystalline solid. Two additional crops of 4.61 and 1.23 g of material were obtained from ethyl acetate and methanol, respectively, by successive evaporations and crystallizations of filtrates. Total yield from all three crops was 22.02 g (88.8% of theory uncorrected for assays) with an additional 1.68 g (~6.8% of

theory) of material obtained from evaporation of the final filtrate. The balance of the product (1.1 g, 4.4%) was believed to be lost during the unoptimized isolation manipulations.

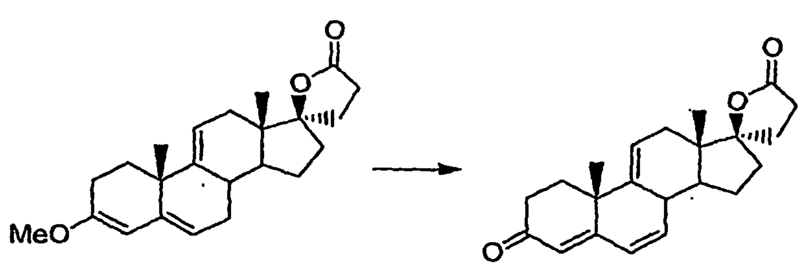
Example 8A: Preparation of (17α)-17-hydroxy-3-oxo-Pregna-4,6,9(11)-triene-21-carboxylic acid γ-lactone (i.e., $\Delta^{9(11)}$-canrenone)



Enol ether substrate (100.0 g) and chloranil (72.2 g) were charged to a 1 L reactor followed by a pre-mixed solution of methylene chloride (200 mL), methanol (120 mL) and water (40 mL) while stirring. The suspension was heated to reflux (42°C) for 2 hours over which time the mixture changed from a yellow suspension to an orange-red homogeneous solution. The reaction was checked for completion using LC. After the reaction was complete, the solution was cooled to room temperature and a solution of 20% sodium metabisulfate (30 mL) was added. The resulting mixture was stirred for 30 minutes. Water (490 mL) was added and the resulting biphase was stirred for 30 minutes. The dihydroquinone byproduct precipitated in the organic phase. The entire biphase was filtered to separate the precipitated dihydroquinone byproduct and the cake was washed twice with methylene chloride (70 mL each wash). The residual aqueous phase was removed from the filtrate and the organic phase was transferred back to the reactor for removal of the remaining dihydroquinone byproduct. The

remaining byproduct was removed by contacting the residual organic phase with pulverized KOH (6.6 g) suspended in methylene chloride (70 mL) with stirring. The suspension was stirred for 1 hour and filtered to remove the dihydroquinone salt byproducts. The byproduct cake was washed twice with methylene chloride (66 mL each wash). Steroid product present in the filtrate was then isolated as described below. Prior to crystallization, the organic phase from above was washed twice with water (300 mL each wash). The mixture was then distilled at atmospheric pressure to remove methylene chloride. Methanol (379 mL) was then added and distillation was continued until the pot temperature reached 65° to 75°C. Additional methanol (35 mL) was added and the mixture was cooled to 40°C. Water (500 mL) was added over 1 hour. The suspension was then cooled within the range of 3°C to 15°C and held for 30 minutes. The solids were filtered and washed with a solution of methanol/water (1:1 v/v, 250 mL). Solids were dried at 70°C in a vacuum oven with a nitrogen bleed until constant weight was obtained. Isolated 88.0 g product (92.1% molar yield unadjusted for assay).

<u>Example 8B</u>: Preparation of (17α)-17-hydroxy-3-oxo-Pregna-4,6,9(11)-triene-21-carboxylic acid γ-lactone (<u>i.e.</u>, $\Delta^{9(11)}$-canrenone)

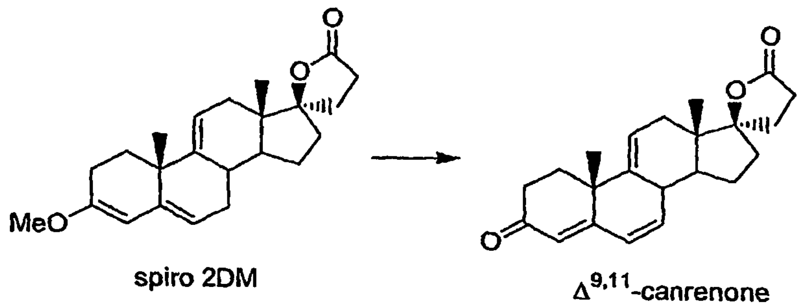


spiro 2DM $\qquad$ $\Delta^{9,11}$-canrenone

Enol ether substrate (50.1 g), acetone (200 mL) and water (50 mL) were charged to a 1-liter, 3-necked round-

bottomed flask equipped with magnetic stirring. The resulting mixture was cooled to -4°C and 1,3-dibromo-5,5-dimethylhydantoin (22.1 g) was added in a single charge while maintaining a temperature below 10°C. The reaction was checked for completion with LC. After completion, the reaction was quenched with ethyl vinyl ether (2.5 mL). The reaction was poured onto $NaHCO_3$ (100 mL of ½ sat. aq. solution) and ethyl acetate (150 mL) was added. The biphase was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The organic phases were combined and washed twice with water (200 mL each wash). The solution was concentrated to approximately 100 g. DMF (25 mL) was added and the resulting solution was charged to a 500 mL, 3-necked round-bottomed flask containing DABCO (19.4 g) in DMF (50 mL) heated to 70°C. After the addition, residual material was rinsed into the reaction flask with additional DMF (75 mL). The reaction was heated to 70°C for 2 hours then cooled to room temperature and poured onto water (200 mL). Methylene chloride (200 mL) was added and the biphase was separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with 5% H_2SO_4 (200 mL) then water (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford an orange oil. Methanol (75 mL) was added to the oil and the mixture was heated to dissolve all solids and oils. The product crystallized and was isolated by filtration at 5°C to afford 37.2 g of yellow solid (75% assay adjusted molar yield).

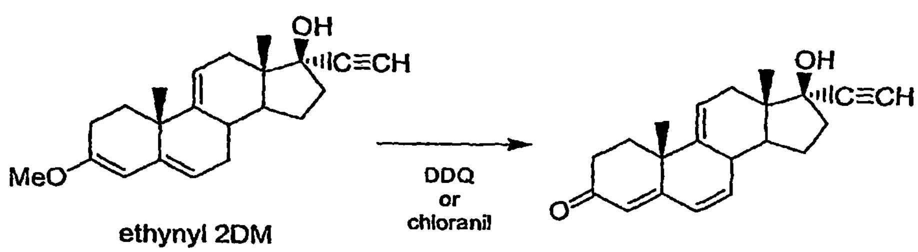
Example 8C: Preparation of (17α)-17-hydroxy-3-oxo-Pregna-4,6,9(11)-triene-21-carboxylic acid γ-lactone (i.e., $\Delta^{9(11)}$-canrenone)



Enol ether substrate (5.0 g), acetone (20 mL) and water (5 mL) were charged to a 50 mL, 3-necked round-bottom flask equipped with a magnetic stirrer. The resulting mixture was cooled to -4°C and 1,3-dibromo-5,5-dimethylhydantoin (2.2 g) was added in a single charge while maintaining the temperature below 10°C. The reaction was monitored by LC for completion. After completion, the reaction was quenched with ethyl vinyl ether (0.25 mL). The reaction was poured onto $NaHCO_3$ (10 mL of ½ sat. aq. solution) and ethyl acetate (15 mL) was added. The biphase was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The organic phases were combined and washed twice with water (20 mL each wash). The solution was concentrated to approximately 10 g. DMF (2 mL) was added and the resulting solution was charged to a 50 mL, 3-necked round-bottomed flask containing Li_2CO_3 /LiBr (1.3 g each) in DMF (5 mL) heated to 70°C. After the addition, residual material was rinsed into the reaction flask with additional DMF (8 mL). The reaction was heated to 70°C for 2 hours then cooled to room temperature and poured onto water (25 mL). Methylene chloride (25 mL) was added and the biphase was separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed three times with water (25 mL each wash). The organic layer was dried ($MgSO_4$),

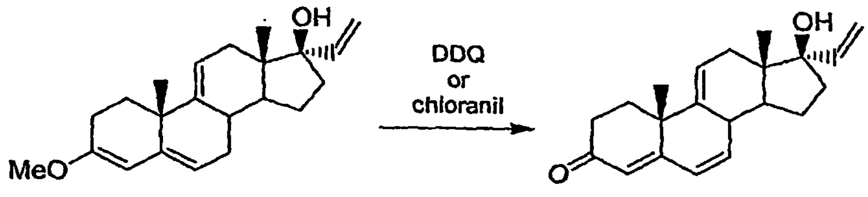
filtered and concentrated to afford a yellow oil. Methanol (75 mL) was added to the oil and the mixture was heated to dissolve all solids and oils. The product crystallized and was isolated by filtration at 5°C to afford 4.0 g of yellow solid (83% molar yield unadjusted for assay).

Example 9: Scheme 4, Step 2: Oxidation of Ethynyl 2DM



17-ethynyl 2DM (30.00 g) was dissolved in acetone (309 mL) and water (17.1 mL) and chilled to -15°C while stirring under nitrogen. DDQ (22.42 g) was added while maintaining the temperature below -10°C. The mixture was stirred for 15 min after addition was complete. The reaction was then quenched by slowly adding saturated $NaHSO_3$ (32.2 mL) with stirring for 30 minutes before concentrating the product mixture. The product mixture was filtered with methylene chloride (350 mL) to recover a solid product which was further washed with methylene chloride. The filtrate was then combined with the washings and extracted three times with water (150 mL, pH 8, Na_2CO_3) followed by an additional extraction with brine (150 mL). The organic layer was dried with Na_2SO_4 and filtered over cartridge grade Magnesol (30 g). After concentration, 27.55 g (96.6% of theory) of pale yellow crystal product were obtained.

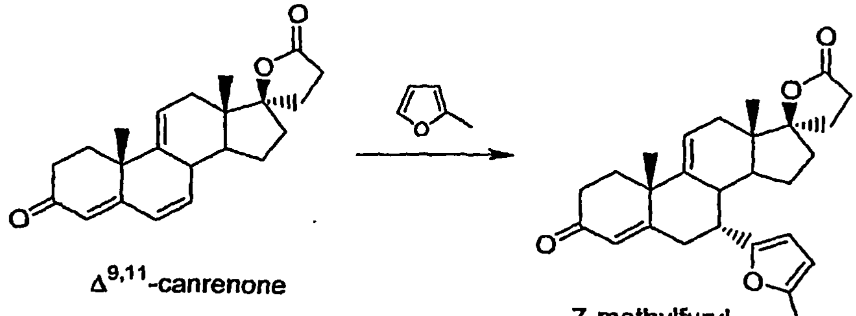
Example 10: Scheme 2, Step 3: 6,7 oxidation of vinyl 2DM



vinyl 2DM

A solution of vinyl 2DM (25.0 g), water (10 mL) and methanol (200 mL) was added to chloranil (19.9 g). The solution was stirred under nitrogen at 42°C for 1 hour. After cooling the mixture to room temperature, 10% aqueous $Na_2S_2O_5$ (7.3 mL) was added at a slow rate and stirred for another 20 minutes. Evaporation yielded a solid comprising a crude product. Methylene chloride (80 mL) was added to the crude product and the mixture was chilled to -10°C before filtering. The filtered solid was washed twice with methylene chloride (20 mL each wash). The filtrate was concentrated and washed to 25 ml and add pulverized KOH (1.65 g). Stir at room temperature for 1.5 hours, filter and wash cake two times with methylene chloride (20 mL). Extract filtrate and washes three times with water and one time with brine. Concentration of the organic phase yielded a pale yellow crystalline product (22.1 g, 92.4%).

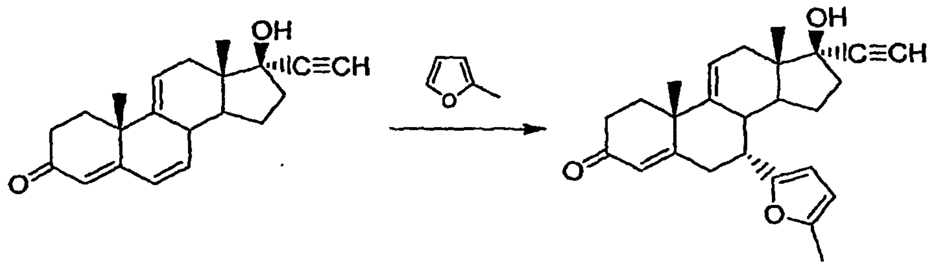
Example 11: Furylation of (17α)-17-hydroxy-3-oxo-Pregna-4,6,9(11)-triene-21-carboxylic acid γ-lactone (i.e., $\Delta^{9(11)}$-canrenone)



$\Delta^{9,11}$-canrenone

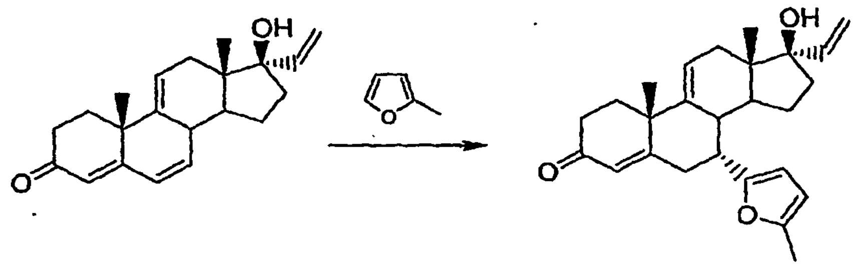
7-methylfuryl

Example 12: Scheme 6, Step 3: Furylation



Boron trifluoride etherate (15.0 mL) was added over 30 minutes to a mixture of 3-keto, 17-ethynyl substrate (24.43 g), ethanol (6.24 g), 2-methylfuran (14.82 g), and dry acetonitrile (140 mL) at a temperature of -9°C. The suspension was stirred for 16.5 hours at a temperature of -10°C. The resulting red-orange homogeneous solution was quenched by the addition of triethylamine (21 mL) and concentrated to 56 g by rotary evaporation. The residue was partitioned between of aqueous NaOH (ca. 7%, 150 mL) and toluene (150 mL). The aqueous phase was re-extracted with toluene (50 mL) and the combined organic phases were washed with 3 N HCl (100 mL) and brine (50 mL) and dried b (Na_2SO_4). Concentration to about 50 g followed by addition of MTBE (50 mL) and hexanes (50 mL, portion-wise) afforded 23.33 g of light yellow crystals after filtration, washing with 2:1 hexanes/MTBE, and drying in vacuo overnight at 60°C. Analysis by ^{1}H NMR and HPLC (uncorrected area) was consistent about 95.5 wt% purity (ca. 4.5 wt% total of toluene and MTBE). Concentration of the filtrates to an orange oil and addition of diethyl ether afforded, after drying at 60C under vacuum, an additional 1.41 g of PHA-711303 as a white crystalline powder containing about 4 wt% Et_2O. 23.6 g (76.4% of theory) of product was obtained.

Example 13: Furylation



Boron trifluoride etherate (0.59 mL, 4.7 mmol) was added to a -10 °C solution of 3-keto, 17-vinyl substrate (1.00 g), 2-methylfuran (0.535 g), and ethanol (0.245 g) in acetonitrile (10 mL). After stirring 19 h at -10 °C, the red reaction solution was quenched by the addition of triethylamine (0.59 g, 5.8 mmol). The mixture was partitioned between about 75 mL of dichloromethane and 7 mL of water. The phases were separated and the organic phase was washed with aqueous saturated NaCl. The resulting organic phase was dried over sodium sulfate and evaporated under reduced pressure. Addition of propyl acetate to the resulting residue afforded a white precipitate. The product mixture was filtered, evaporated and diethyl ether was added to give 0.38 g of a yellow crystalline product.

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In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained. As various changes can be made in the above processes and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

O. A process for preparing a 17-spirolactone steroid compound, the process comprising:

carbonylating a steroid substrate wherein the substrate is substituted at the C-17 position with a first substituent selected from the group consisting of hydroxy and protected hydroxy; and a second substituent selected from the group consisting of alkenyl and alkynyl.

O1. A process as set forth in claim O, wherein the steroid substrate is substituted at the C-17 position with a first substituent comprising a hydroxy group and a second substituent comprising an alkenyl or an alkynyl group.

O2. A process as set forth in claim O1, wherein the steroid substrate comprises a 17-alkenyl-17-hydroxy steroid or a 17-alkynyl-17-hydroxy steroid.

O3. A process as set forth in claim O2, wherein the process comprises:

reducing the 17-alkynyl group of a 17-alkynyl-17-hydroxy steroid compound to produce a 17-alkenyl-17-hydroxy steroid compound; and

carbonylating the 17-alkenyl-17-hydroxy steroid compound to produce said 17-spirolactone steroid compound.

O4. A process as set forth in claim O3, wherein the 17-alkynyl-17-hydroxy steroid compound is contacted with a source of hydrogen to reduce the 17-alkynyl group and yield an intermediate comprising the 17-alkenyl-17-hydroxy steroid compound; and

contacting the 17-alkenyl-17-hydroxy steroid compound with a source of carbon monoxide and a carbonylation catalyst to yield the 17-spirolactone product.

05. A process as set forth in claim 04, wherein the 17-alkynyl group is reduced in the presence of a catalyst.

06. A process as set forth in claim O, wherein the process comprises:

carbonylating a 17-alkynyl-17-hydroxy steroid compound to produce a steroid intermediate comprising a 17-lactenone steroid compound; and

reducing the 17-lactenone steroid compound to produce a 17-spirolactone steroid compound.

07. A process as set forth in claim 06, wherein the process comprises contacting the 17-alkynyl-17-hydroxy steroid compound with a source of carbon monoxide and a carbonylation catalyst to yield the intermediate comprising the 17-lactenone steroid compound; and

contacting the 17-lactenone steroid compound with a source of hydrogen to reduce the 17-lactenone group to yield the 17-spirolactone steroid product.

08. A process as set forth in claim 07, wherein the 17-lactenone steroid compound is reduced in the presence of a catalyst.

09. A process as set forth in any of the preceding claims, wherein the carbonylation catalyst is formed by contacting a source of a metal with a source of carbon monoxide.

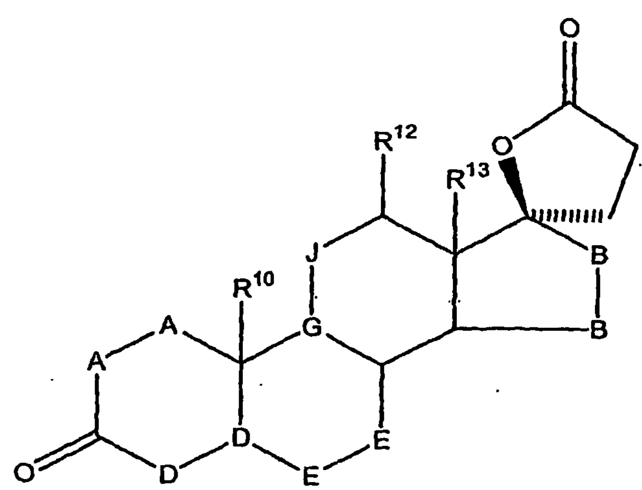
010. A process as set forth in claim 09, wherein the carbonylation catalyst is formed by contacting a source of metal with a source of carbon monoxide in the presence of a ligand.

011. A process as set forth in claim 09 or 010, wherein the carbonylation catalyst is formed in the presence of a reducing agent.

012. A process as set forth in claim 09, wherein the carbonylation catalyst is formed <u>in situ</u> in the carbonylation reaction medium.

013. A process as set forth in any of claims 09 to 013, wherein the carbonylation catalyst comprises a metal selected from the group consisting of Co, Ni, Fe, Pt, Pd, Ru, Rh, Ir and mixtures thereof.

A. A process for the preparation of a compound corresponding to the Formula 1503:



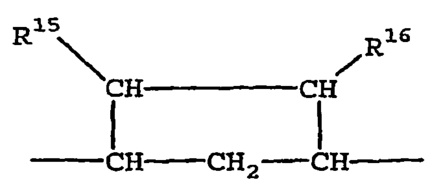
wherein

R^{10}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, hydroxy,

alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano and aryloxy;

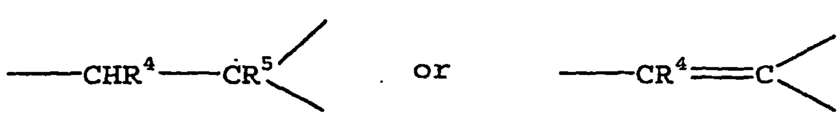
A-A represents the group CHR^1-CHR^2 or CR^1=CR^2, where R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^1 and R^2 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

B-B represents the group CHR^{15}-CHR^{16} or an alpha- or beta- oriented group:



where R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, and aryloxy;

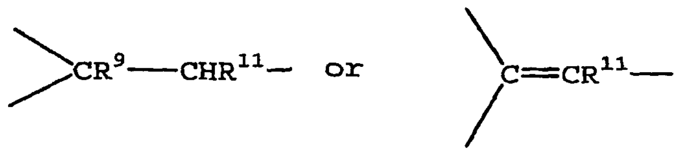
D-D represents the group



where R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^4

and R^5 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

G-J represents the group

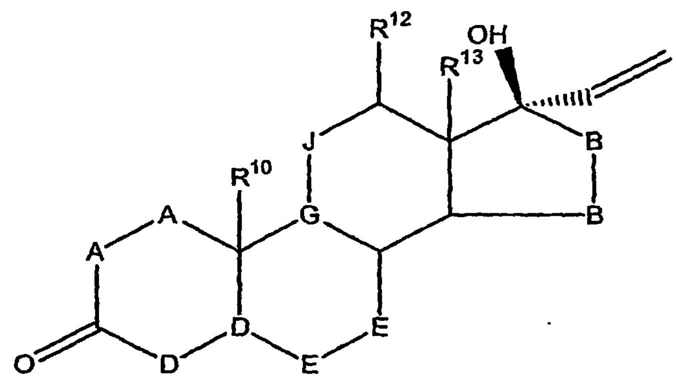


where R^9 and R^{11} are independently selected from the group consisting of hydrogen, hydroxy, protected hydroxy, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^9 and R^{11} together form an epoxy group;

E-E represents the group $-CHR^6-CHR^7-$ or $-CR^6=CR^7-$, wherein R^6 and R^7 are independent, R^6 being selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy, and R^7 being selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, aryloxy, heteroaryl, heterocyclyl, thioacetyl, furyl and substituted furyl,

the process comprising:

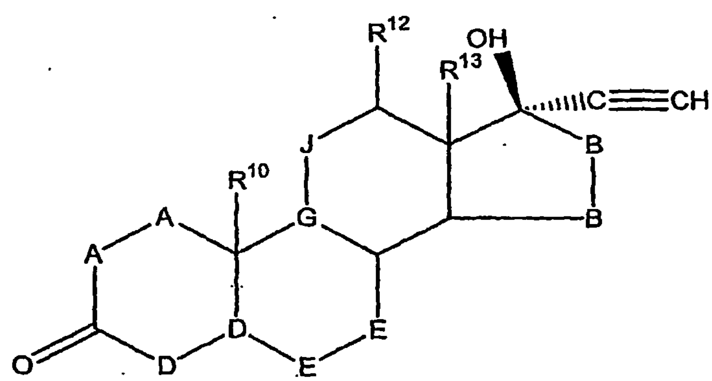
carbonylating a 17-vinyl-17-hydroxy steroid compound of Formula 1502:



wherein R^{10}, R^{12}, R^{13}, A-A, B-B, D-D, G-J and E-E are as defined above.

A1. A process as set forth in claim A, wherein the process further comprises:

preparing the compound of Formula 1502 by reducing the 17-ethynyl group of a compound of Formula 1501 to a 17-vinyl group, said compound of Formula 1501 having the structure:



where the substituents R^{10}, R^{12}, R^{13}, A-A, B-B, D-D, G-J and E-E are as defined above in Formula 1503.

A2. A process as set forth in claim A wherein said compound of Formula 1501 is contacted with a source of hydrogen in a hydrogenation reaction zone, thereby reducing the 17-ethynyl group and yielding an intermediate comprising the 17-vinyl compound corresponding to Formula 1502; and

contacting the derivative of Formula 1502 with a source of carbon monoxide and a carbonylation catalyst in a carbonylation reaction zone to yield the product of Formula 1503.

A3. A process as set forth in claim A2, wherein said compound of Formula 1501 is contacted with a source of hydrogen in the presence of a catalyst.

A4. A process as set forth in claim A2, wherein said intermediate derivative of Formula 1502 is removed from said hydrogenation reaction zone and transferred to said carbonylation reaction zone.

A5. A process as set forth in claim A, wherein said compound of formula 1503 is simultaneously contacted with a source of hydrogen, a source of carbon monoxide and a catalyst system effective for reducing the 17-ethynyl group of the compound of formula 1503 to a 17-vinyl group and for carbonylating the resulting derivative of formula 1502 <u>in situ</u> to convert the 17-hydroxy-17-vinyl structure thereof to a 17-spirobutyrolactone structure.

A6. A process as set forth in any of the preceding claims wherein the hydrogenation reaction is conducted in the presence of an alkene or cycloalkene.

A7. A process as set forth in claim A4 wherein said alkene or cycloalkene function as a solvent for said compound of formula 1503.

A8. A process as set forth in claim A5 wherein said alkene or cycloalkene further functions as a solvent for said compound of formula 1502.

A9. A process as set forth in claim A4 or A5 wherein said alkene or cycloalkene functions as a solvent for the product compound of formula 1501.

A10. A process as set forth in any of the preceding claims wherein the 17-ethynyl group is reduced to a 17-vinyl group in a hydrogenation reaction zone in the presence of a sacrificial hydrogenation target, thereby inhibiting the hydrogenation of the 17-vinyl group to a 17-ethyl group.

A11. A process as set forth in any of claims A1 through A8 wherein reduction of said 17-ethynyl group comprises contacting said compound of formula 1503 with a source of hydrogen in the presence of a noble metal catalyst.

AA. A process as set forth in claim A11 wherein the catalyst comprises Pd on a calcium carbonate support.

A12. A process as set forth in any of claims A1 through A11 wherein hydrogenation of said 17-ethynyl group is conducted at a temperature of from about 0° to about 100°C.

A13. A process as set forth in claim A12, wherein said hydrogenation is conducted a temperature of from about 25° to about 75°C.

A14. A process as set forth in any of claims A1 through A13 wherein hydrogenation of said 17-ethynyl group is conducted at a pressure of from about 0 to about 100 psig.

A15. A process as set forth in claim A14, wherein said hydrogenation is conducted at a pressure of from about 25 to about 50 psig.

A16. A process as set forth in any of the preceding claims in which said carbonylation catalyst is formed by contacting a source of a metal with a source of carbon monoxide.

A17. A process as set forth in claim A16, wherein the carbonylation catalyst is formed by contacting the a source of metal with a source of carbon monoxide in the presence of a ligand.

A18. A process as set forth in claim A16 or A17, wherein the carbonylation catalyst is formed in the presence of a reducing agent.

A19. A process as set forth in claim A16, wherein the carbonylation catalyst is formed <u>in situ</u> in the carbonylation reaction medium.

A20. A process as set forth in any of claims A16 to A19, wherein the carbonylation catalyst comprises a metal selected from the group consisting of Co, Ni, Fe, Pt, Pd, Ru, Rh, Ir and mixtures thereof.

A21. A process as set forth in claim A18 wherein said carbonylation catalyst is formed by contacting a source of Pd, a ligand and a reducing agent.

A22. A process as set forth in any of claims A17 to A21, wherein the ligand comprises phosphorus.

A23. A process as set forth in any of claims A17 to A22, wherein the reducing agent comprises an active hydrogen source.

A24. A process as set forth in claim A23, wherein the reducing agent is selected from the group consisting of hydrogen, formic acid, borohydrides and oxalic acid.

A25. A process as set forth in claim A24, wherein the reducing agent comprises formic acid.

A26. A process as set forth in any of the preceding claims wherein said intermediate of formula 1502 is contacted with carbon monoxide at a temperature of from about 80° to about 150°C.

A27. A process as set forth in claim A26, wherein said intermediate of formula 1502 is contacted with carbon monoxide at a temperature of from about 100° to about 105°C.

A28. A process as set forth in any of claims A, A1, A2 or A3 through A27 comprising:

contacting said compound of formula 1503 with a source of hydrogen and a hydrogenation catalyst in a liquid reaction medium comprising a solvent, thereby producing a hydrogenation reaction mixture comprising a hydrogenation reaction solution comprising said intermediate of formula 1502 in said solvent; and

mixing said hydrogenation reaction solution or a concentrate thereof with water to produce a liquid crystallization medium in which the solubility of said compound of formula 1502 is lower than the solubility thereof in said solvent alone; and

crystallizing said compound of formula 1502.

A29. A process as set forth in claim A28 wherein said hydrogenation reaction solution or concentrate thereof is filtered for removal of catalyst prior to mixing thereof with water.

A30. A process as set forth in any of the preceding claims in which said compound of formula 1502 is contacted with a source of carbon monoxide and a carbonylation catalyst in a liquid reaction medium comprising a solvent for the compound of formula 1502, thereby producing a carbonylation reaction mixture comprising a carbonylation reaction solution comprising said compound of formula 1501.

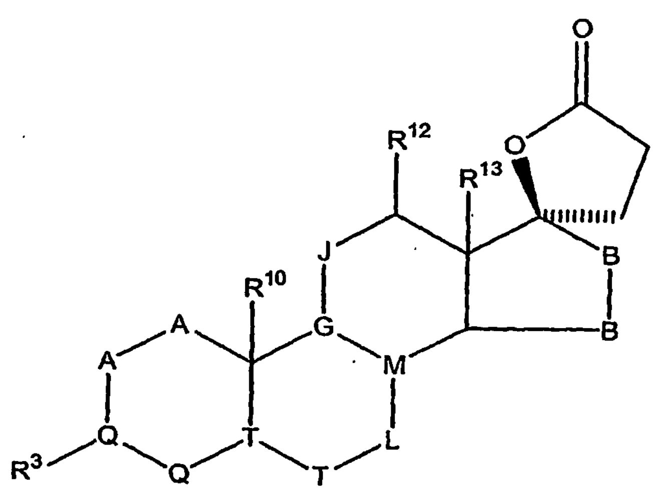
A31. A process as set forth in claim A30 wherein said product of formula 1501 is recovered from a final crystallization medium comprising said carbonylation reaction solution or derived therefrom.

A32. A process as set forth in claim A31 wherein said carbonylation reaction solution is mixed with a solvent that is miscible with the liquid reaction medium but in which the solubility of said compound of formula 1501 is lower than it is in the liquid reaction medium, resulting in crystallization of said compound of formula 1501 from the resulting crystallization medium.

A33. A process as set forth in claim A31 wherein, prior to crystallization of said compound of formula 1501, said carbonylation reaction solution or a concentrate thereof is filtered for removal of any solids contained therein.

A34. A process as set forth in claim A33 wherein solids removed by filtration from said carbonylation reaction solution or concentrate thereof are washed with a solvent which is combined with the filtrate prior to crystallization.

B. A process for the preparation of a compound corresponding to the Formula 2503:



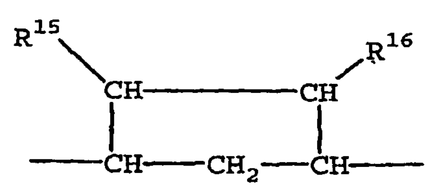
wherein

R^3 is selected from the group consisting of hydrogen, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl and hydroxycarbonyl;

R^{10}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano and aryloxy;

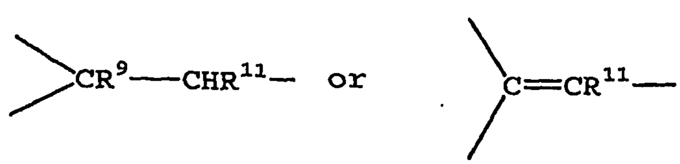
A-A represents the group $-CHR^1-CHR^2-$ or $-CR^1=CR^2-$, where R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy or R^1 and R^2 together with the carbons of the steroid backbone to which they are attached form a cycloalkyl group;

B-B represents the group $-CHR^{15}-CHR^{16}-$ or an alpha- or beta- oriented group:



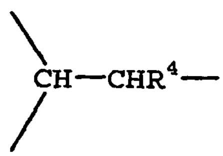
where R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

G-J represents the group

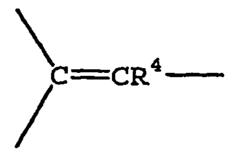


where R^9 and R^{11} are independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

Q-Q represents the group

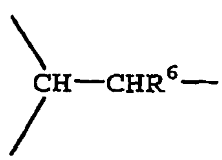


or

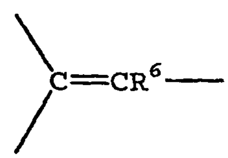


where R^4 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy;

T-T represents the group

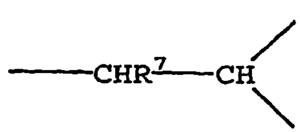


or

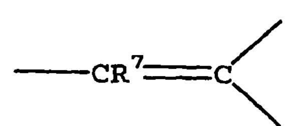


where R^6 is selected from the group consisting of hydrogen, halo, alkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy; and

L-M represents the group



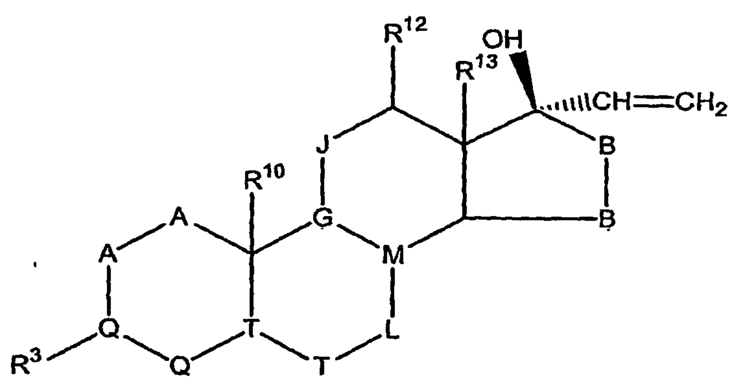
or



where R^7 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl, acyloxyalkyl, cyano, aryloxy, heteroaryl, heterocyclyl, thioacetyl, furyl and substituted furyl,

the process comprising:

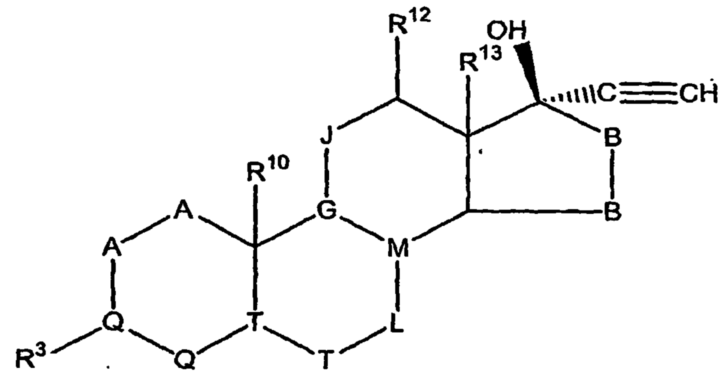
carbonylating a 17-vinyl-17-hydroxy steroid compound of Formula 2502:



where the substituents R^3, R^{10}, R^{12}, R^{13}, A-A, B-B, G-J, Q-Q, T-T and L-M are as defined in Formula 2503.

B1. A process as set forth in claim B, wherein the process further comprises:

preparing the compound of Formula 2502 by reducing the 17-ethynyl group of a compound of Formula 2501 to a 17-vinyl group, said compound of Formula 2501 having the structure:



where the substituents R^3, R^{10}, R^{12}, R^{13}, A-A, B-B, G-J, Q-Q, T-T and L-M are as defined above in Formula 2503.

B2. A process as set forth in claim B wherein said compound of Formula 2501 is contacted with a source of hydrogen in a hydrogenation reaction zone, thereby reducing the 17-ethynyl group and yielding an intermediate comprising the 17-vinyl compound corresponding to Formula 2502; and

contacting the derivative of Formula 2502 with a source of carbon monoxide and a carbonylation catalyst in a carbonylation reaction zone to yield the product of Formula 2503.

B3. A process as set forth in claim B1 or B2, wherein said compound of Formula 2501 is contacted with a source of hydrogen in the presence of a catalyst.

B4. A process as set forth in claim B2 wherein said intermediate derivative of formula 2502 is removed from said hydrogenation reaction zone and transferred to said carbonylation reaction zone.

B5. A process as set forth in claim B2 wherein said compound of formula 2503 is simultaneously contacted with a source of hydrogen, a source of carbon monoxide and a catalyst system effective for reducing the 17-ethynyl group of the compound of formula 2503 to a 17-vinyl group and for carbonylating the resulting derivative of formula 2502 in situ to convert the 17-hydroxy-17-vinyl structure thereof to a 17-spirobutyrolactone structure.

B6. A process as set forth in any of the preceding claims wherein the hydrogenation reaction is conducted in the presence of an alkene or cycloalkene.

B7. A process as set forth in claim B6 wherein said alkene or cycloalkene function as a solvent for said compound of formula 2503.

B8. A process as set forth in claim B7 wherein said alkene or cycloalkene further functions as a solvent for said compound of formula 2502.

B9. A process as set forth in claim B6 or B7 wherein said alkene or cycloalkene functions as a solvent for the product compound of formula 2502.

B10. A process as set forth in any of the preceding claims wherein the 17-ethynyl group is reduced to a 17-vinyl group in a hydrogenation reaction zone in the presence of a sacrificial hydrogenation target, thereby inhibiting the hydrogenation of the 17-vinyl group to a 17-ethyl group.

B11. A process as set forth in any of claim B2 through B10 wherein reduction of said 17-ethynyl group comprises contacting said compound of formula 2503 with a source of hydrogen in the presence of a noble metal catalyst.

BB. A process as set forth in claim B11 wherein the catalyst comprises Pd on a calcium carbonate support.

B12. A process as set forth in any of claims B1 through B11 wherein hydrogenation of said 17-ethynyl group is conducted at a temperature of from about 0° to about 100°C.

B13. A process as set forth in claim B12, wherein said hydrogenation is conducted a temperature of from about 25° to about 75°C.

B14. A process as set forth in any of claims B1 through B13 wherein hydrogenation of said 17-ethynyl group is conducted at a pressure of from about 0 to about 100 psig.

B15. A process as set forth in claim B14, wherein said hydrogenation is conducted at a pressure of from about 25 to about 50 psig.

B16. A process as set forth in any of the preceding claims in which said carbonylation catalyst is formed by contacting a source of a metal with a source of carbon monoxide.

B17. A process as set forth in claim B16, wherein the carbonylation catalyst is formed by contacting the source of metal with a source of carbon monoxide in the presence of a ligand.

B18. A process as set forth in claim B16 or B17, wherein the carbonylation catalyst is formed in the presence of a reducing agent.

B19. A process as set forth in claim B16, wherein the carbonylation catalyst is formed <u>in situ</u> in the carbonylation reaction medium.

B20. A process as set forth in any of claims B16 to B19, wherein the carbonylation catalyst comprises a metal selected from the group consisting of Co, Ni, Fe, Pt, Pd, Ru, Rh, Ir and mixtures thereof.

B21. A process as set forth in claim B18 wherein said carbonylation catalyst is formed by contacting a source of Pd, a ligand and a reducing agent.

B22. A process as set forth in any of claims B17 to B21, wherein the ligand comprises phosphorus.

B23. A process as set forth in any of claims B17 to B22, wherein the reducing agent comprises an active hydrogen source.

B24. A process as set forth in claim B23, wherein the reducing agent is selected from the group consisting of hydrogen, formic acid, borohydrides and oxalic acid.

B25. A process as set forth in claim B24, wherein the reducing agent comprises formic acid.

B26. A process as set forth in any of the preceding claims wherein said intermediate of formula 2502 is contacted with carbon monoxide at a temperature of from about 80° to about 150°C.

B27. A process as set forth in claim B26, wherein said intermediate of formula 2502 is contacted with carbon monoxide at a temperature of from about 100° to about 105°C.

B28. A process as set forth in any of the preceding claims comprising:

contacting said compound of formula 2503 with a source of hydrogen and a hydrogenation catalyst in a liquid reaction medium comprising a solvent, thereby producing a hydrogenation reaction mixture comprising a hydrogenation reaction solution comprising said intermediate of formula 2502 in said solvent; and

mixing said hydrogenation reaction solution or a concentrate thereof with water to produce a liquid crystallization medium in which the solubility of said compound of formula 2502 is lower than the solubility thereof in said solvent alone; and

crystallizing said compound of formula 2502.

B29. A process as set forth in claim B28 wherein said hydrogenation reaction solution or concentrate thereof is filtered for removal of catalyst prior to mixing thereof with water.

B30. A process as set forth in any of the preceding claims in which said compound of formula 2502 is contacted with a source of carbon monoxide and a carbonylation catalyst in a liquid reaction medium comprising a solvent for the compound of formula 2502, thereby producing a carbonylation reaction mixture comprising a carbonylation reaction solution comprising said compound of formula 2501.

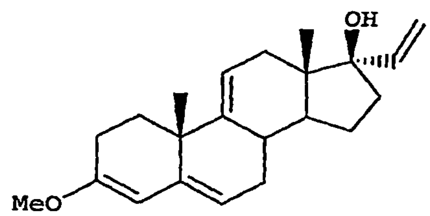
B31. A process as set forth in claim B30 wherein said product of formula 2501 is recovered from a final crystallization medium comprising said carbonylation reaction solution or derived therefrom.

B32. A process as set forth in claim B31 wherein said carbonylation reaction solution is mixed with a solvent that is miscible with the liquid reaction medium but in which the solubility of said compound of formula 2501 is lower than it is in the liquid reaction medium, resulting in crystallization of said compound of formula 2501 from the resulting crystallization medium.

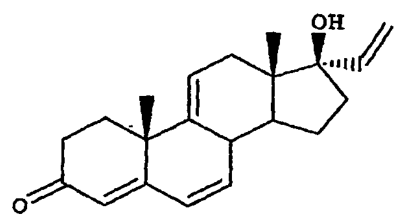
B33. A process as set forth in claim B31 wherein, prior to crystallization of said compound of formula 2501, said carbonylation reaction solution or a concentrate thereof is filtered for removal of any solids contained therein.

B34. A process as set forth in claim B33 wherein solids removed by filtration from said carbonylation reaction solution or concentrate thereof are washed with a solvent which is combined with the filtrate prior to crystallization.

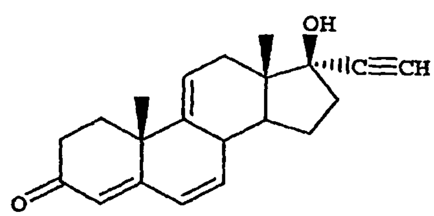
C. A compound corresponding to Formula A:



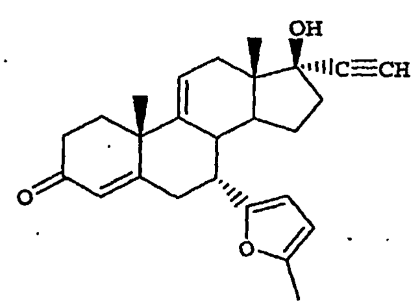
C1. A compound corresponding to Formula B:



C2. A compound corresponding to Formula C:



C3. A compound corresponding to Formula D:



C4. A compound corresponding to Formula E: